Effects of DBS-STN on Impulsivity and Other Psychiatric Symptoms in Parkinson's Disease

Outcomes of a Prospective Multicentre Observational Study, a Narrative Review and a Single Site Audit

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Submitted for the degree of

Doctor of Philosophy

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I. Abstract

This thesis has utilised the data collected in the **C**linical **R**esponse of **I**mpulsivity to Deep Brain **S**timulation in **P**arkinson's Disease (**CRISP**) study. The CRISP study is a prospective observational multicentre study established to understand, explore, and examine one of the most frequently asked questions in deep brain stimulation (DBS) clinics: Whether DBS worsens impulsive behaviours in Parkinson's disease (PD) patients. Impulsive behaviours are commonly reported among PD patients and are commonly considered to be a side effect of anti-Parkinson's medication. As a PhD student, I established the CRISP study with a team of experienced multidisciplinary clinicians and PD nurses from seven DBS clinics across the UK, who maintained the collaboration during the COVID-19 pandemic to provide insight into this ongoing and lingering debate. Participants in the CRISP study are asked to complete a set of self-rated and clinician-rated questionnaires. These scales assess psychiatric symptoms, motor symptoms, quality of life, personality traits and carer[1] burden and are administered once before DBS activation and three, six and twelve months subsequently. Because of reasons that are explained in detail later in this chapter, only data collected up to the 6 months after the operation is analysed and presented here.

The clinical response of impulsive behaviours following DBS was the primary outcome of the CRISP Study and the current thesis. However, changes in other measured psychiatric symptoms are also discussed as secondary outcomes. Lastly, the burden on carers is reviewed among the cohort. In addition to the CRISP study, I have conducted a single-centre retrospective review as part of a clinical audit. This retrospective review examines clinical notes in the database of one of the participating DBS centres, King's College Hospital. This was to compare the prevalence and course of psychiatric symptoms (if any) within a similar cohort between a prospective study with multiple assessment tools (The CRISP study) and a retrospective study reviewing routine clinical notes. This thesis is divided between 4 parts, with 7 chapters in between. In the chapter 1, an introduction on Parkinson's disease prevalence, pathology, risk factors and prevalence of psychiatric symptoms are presented. Later in the chapter, DBS has been discussed as an alternative therapy for Parkinson's disease and its relationship with impulsivity. In *Chapter 2*, a narrative review is presented, which was

[1] 'Caregiver' is another common synonym used in literature.

conducted for the current literature on the effects of DBS therapy on psychiatric symptoms in Parkinson's disease. Various themes are utilised to stratify the results, including early and long-term outcomes for various psychiatric symptoms (like psychosis, mood, suicidality, apathy, impulsivity, and personality traits). Two sections are also included to review the results of studies that have examined the impact of DBS parameters on psychiatric symptoms and compared the effects of DBS targets on psychiatric symptoms in Parkinson's disease.

Furthermore, details of the background, rationale, methodology and materials and results of the CRISP study are presented in the *chapter 3*. The main findings of the CRISP study at 6-month follow-up include significant improvement in impulsivity total scores on the QUIP-RS, hypersexuality and hobbyism-punding, with compulsive shopping showing a trend towards a significant improvement. At baseline, anhedonia showed a predictive value for significantly improving total impulsivity scores. Anhedonia, along with the elation scores, predicted the improvement in hypersexuality.

Additionally, there was a significant reduction in total LEDD and anxiety, but the depression did not improve significantly, and apathy significantly worsened. Personality traits showed a significant increase in traits related to impulsivity. Lastly, the carer burden was significantly reduced. As for the retrospective review, the main findings were the significantly older age of the retrospective cohort and lower frequency of psychiatric symptoms compared to the matched CRISP cohort. In the *chapter 4*, the rationale, objective, methodology, results and the translational outcomes of the single site audit are presented. In the *chapter* 5 a discussion is presented in the context of the results of the CRISP study, the narrative review and the audit. For the CRISP study, the relevance of the characteristics of participants, including age, gender, and ethnicity, is discussed. Moreover, the improvement in impulsivity is discussed in the cognitive and psychosocial contexts. The non-significant changes in gambling, binge eating and dopamine dysregulation syndrome are also discussed relying on different neuropsychological contexts. Lastly, other psychiatric outcomes are discussed in detail. As for the retrospective review, it is discussed how adding brief, valid questionnaires can improve the pre-DBS screening process without burdening DBS clinics. Finally, I have added a section in the discussion chapter on the pandemic's impacts on my thesis and the CRISP study. I briefly discussed how an observational multicentre study could be 'pandemic proof' in the future based on my experience. The conclusion and summary points are presented in the *chapter 6*.

II. Acknowledgement

I enrolled in the current PhD program more than 4 years ago. I believed that it will ultimately help me develop personally and become an academic psychiatrist. I never thought I would have to do that while the world, my country, and my family are facing some of the most difficult events: A catastrophic pandemic that took my mom as a victim, deadly and destabilizing conflicts that put my country in a state of shock and fear during the whole year of 2020, a war in Europe that shook the world economy, deadly earthquakes in Kurdish cities in Turkey and many more nearly unprecedentedly consequent events, on a regional and global scale. Nevertheless, the investment was right, and there is no better time than when the determination is the strongest. That said, it would not have been possible to endure consequent events and move forwards without having full support and love of my wife, Golizar. There are no scales that are valid and precise enough to quantify my gratitude for having her by my side. So, I am not going to pretend that I know its magnitude, but I can relate it to my growing resilience towards setbacks, and excitement for new adventures. On an academic level, my supervisor, Dr Paul Shotbolt, is the second person to whom I would like to extend my appreciation and thanks. Without a doubt, I could not ask for a better and more resourceful supervisor who remains available, supportive, and understanding every week in and week out.

Furthermore, I cannot end this piece without thanking my second supervisor and the chief investigator for the study, Dr David Okai, who remained an available and reliable support for academic matters throughout my journey. All other research members of the CRISP study, including my third supervisor, Professor Michael Samuel, cannot be left out here. They truly supported me from the start and maintained their support over time. Finally, I want to thank everyone at IoPPN and KCH who helped in various ways to make this journey as smooth and joyful as possible.

III. COVID-19 Impact Statement

The CRISP study on which my thesis was planned to be based in March. 2020 was strictly affected by the lockdown. Several factors in the study made it more prone to lockdown and COVID crisis. Firstly, as a multicentre study, it required multiple online meetings between all seven participating DBS centres. However, the meetings were scheduled less frequently than required due to other priorities related to COVID and lockdown. Therefore, completing the protocol lasted longer than usual. In the same process, several factors were unclear to plan for, such as the commencement and end date of the study. This is because it was not known when the operation would resume. For the CRISP study, it was the most critical point as the PD patients who undergo DBS operation were planned to be recruited. Secondly, several questionnaires used in the CRISP study required permission from copywrite owners.

In some cases, their response was unusually long and required frequent follow-ups. In the follow-up, the delay was justified by the overwhelming impacts of the lockdown on the institutes. Thirdly, receiving the Research Ethics Committee (REC) approval, and the research and development department (R&D) approval from participating DBS centres lasted several months longer than usual. The research team was informed that this is mainly due to a staff shortage or prioritization of COVID-related studies.

After receiving the REC approval from seven participating centres, only 2 started recruiting. The research team were informed that there is a shortage of staff in the lingering DBS centres, and the R&D is prioritizing other studies to review. Finally, when all centres started recruiting, the surgery slots were very limited due to backlog, shortage of available beds, and shortage of staff. Therefore, instead of recruiting the expected 10 patients per month, only 2-3 patients were recruited per month from 10-2021 to 10-2022. Furthermore, the new post-COVID protocol and guidelines in participating centres caused some patients to be given very short notice for the next available surgery slot. This left me much less time to complete the baseline data collection. As a result, several potential participants were missed. To compensate for the time missed, a few amendments were requested, such as changing the recruitment window and the end date for recruitment (See *Appendix 10* and *11*). This was done to have more time to complete baseline recruitments and increase the number of recruits. The efforts to recruit many participants deemed sufficient for this thesis shortened the period for data analysis and writing up the thesis.

IV. Abbreviations

Abbreviations in Text	
AD	*Alzheimer's Disease*
AEs	*Adverse Events*
AES	*Apathy Evaluation Scales*
AMI	*Apathy Motivational Index*
ASBPD	*Ardouin Scale of Behaviour in Parkinson's Disease*
BAI	*Beck's Anxiety Inventory*
BDI	*Beck's Depression Inventory*
BIS	*Barratt Impulsiveness Scale*
BMT	*Best Medical Treatment*
CBT	*Cognitive Behavioural Therapy*
CI	*Chief Investigator*
CI	*Confidence Interval*
CRISP	*Clinical Response of Impulsive Behaviours to Deep Brain Stimulation in Parkinson's Disease*
COMT	*Catechol-O-Methyl Transferase*
CSSRS	*Columbia-Suicide Severity Rating Scale*
CSSRS	*Columbia-Suicide Severity Rating Scale*
DA	*Dopaminergic Agent*
DAT	*Dopamine Transporters*
DAWS	*Dopamine Agonist Withdrawal Syndrome*
DBS	*Deep Brain Stimulation*
DDS	*Dopamine Dysregulation Syndrome*
DLPFC	*Dorsolateral Prefrontal Cortex*
DOMINION	*Impulse Control Disorders in Parkinson's Patients Treated with Pramipexole and Other Agents*

Abbreviations in Text	
DRT	*Dopamine Replacement Therapy*
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EARLYSTIM	*Deep Brain Stimulation in Early Patients with Parkinson's Disease – Trial Study*
EQ-5D-5L	*European Quality-5 Dimension – 5 Level*
EQ-VAS	*European Quality-visual analogue scale*
FDG -PET	*F-Fluorodeoxyglucose – Positron Emission Tomography*
GABA	*Gamma-aminobutyric acid*
GAD-7	*General Anxiety Disorder – 7 Item*
GPe	*Globus Pallidum externa*
GPi	*Globus Pallidum interna*
HAM-A	*Hamilton Anxiety Scale*
HAM-D	*Hamilton Depression Scale*
ICBs	*Impulsive Compulsive behaviours*
ICDs	*Impulsive Control Disorders*
IOPPN	*Institute of Psychiatry, Psychology and Neuroscience*
KCL	*King's College London*
KCH	*King's College Hospital*
LEDD	*Levodopa Equivalent Daily Dose*
LARS	*Lille Apathy Rating Scale*
MADRS	*Montgomery–Åsberg Depression Rating Scale*
MAO-B	*Monoamine Oxidase B*
MDMQ	*Multidimensional Mood State Questionnaire*
MDS-UPDRS	*Movement Disorders Society – Unified Parkinson's Disease Rating Scale*
MCI	*Mild Cognitive Impairment*
MIDI	*Minnesota Impulse Disorders Interview*
MRI	*Magnetic Resonance Imagine*

Abbreviations in Text	
N.	*Total Number of participants in cohort*
n.	*number of participants in subgroup*
NIHR	*National Institute for Health Research*
NMSQ	*Non-Motor symptoms questionnaire*
NMSS	*Non-Motor Symptoms Scale*
NPI-12	*Neuropsychiatry Inventory – 12 Items*
OFC	*Orbitofrontal Cortex*
RCT	*Randomized Clinical Trial*
non-RCT	*Non-Randomized Clinical Trial*
PANAS	*Positive and Negative Affect Schedule*
PD	*Parkinson's Disease*
PDQ-9	*Parkinson's Disease questionnaires 9 items*
PHQ-9	*Patient Health Questionnaire – 9 items*
PICS	*Parkinson's Impulsive-Control Scale*
POMS	*Profile of Mood Scale*
PPI	*Patient and Public Involvement*
PREDI-STIM	*Predictive Factors and Subthalamic Stimulation in Parkinson's Disease – Observational Study*
QUIP	*Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease*
QUIP-RS	*Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease -Revised*
RF	*Research Fellow*
SCID-II	*Structured clinical interview for DSM-IV Personality disorder*
SD	*Standard Deviation*
SHAPS	*Snaith-Hamilton Pleasure Scale*
SLaM	*South London and Maudsley NHS Foundation Trust*
SN	*Substantia Nigra*
SSI	*Scale for Suicidal Ideation*

Abbreviations in Text	
STN	*Subthalamic Nucleus*
STAI	*State-Trait Anxiety Inventory*
STROBE	*Strengthening The Reporting of Observational Studies in Epidemiology*
TEED	*Total electrical energy delivered*
UPDRS	*Unified Parkinson's Disease Rating Scale*
UPPS-P	*Urgency, Premeditation, Perseverance, Sensation seeking and Positive urgency Impulsive Behaviour Scale*
VAMS	*Visual Analogue Mood Scales*
VIM	*Ventralis intermediate nucleus*
WSAS	*Work and Social Adjustment Scale*
ZBI	*Zarit Burden Interview*
People	
AA	*Arteen Ahmed*
CW	*Camille Wratten*
DO	*David Okai*
MB	*Mathew Butler*
PS	*Paul Shotbolt*

V. Declaration of Thesis

I hereby declare the work within this thesis is my own unless explicitly referenced to the work of others. All materials are used with the formal consent of copywriters, or they are in the public domain and free to use for academic purposes. The contents are original, and I have not submitted the thesis or any work therein for a degree at another university.

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VIII. Table of Contents

Chapter 1: Parkinson's, Neuropsychiatric Symptoms and Brain Stimulation

1.1. Parkinson's Disease

Parkinson's disease (PD) is a complex neurological disorder and the second most common neurodegenerative disorder that affects 1-3% of people over the age of 65 and 5% of people over the age of 80 (Cerri et al., 2019). The estimated public rate of 0.3% indicates a significant increase in the PD rate with age (Clarke, 2007). The clinical presentation of PD is generally diverse, with a range of motor and non-motor symptoms. The extensive neurodegeneration of different parts of the nervous system with multiple neurotransmitter involvement is the main cause of this heterogeneity (Kalia & Lang, 2015). Multidimensional data-driven clusters are ideal for understanding such a complex disorder. However, an empirical classification will be considered here to investigate the relationships between symptoms as an endpoint. Empirical classifications are based on clinical observation. The CRISP study, which focuses on the clinical response of psychiatric symptoms of PD to treatment, is more suited to this approach. Empirical classifications of PD may classify patients based on motor and non-motor symptoms and age of onset (Marras & Chaudhuri, 2016). These symptoms are entities that will be examined and discussed in this thesis as potential predictors for the clinical response of impulsive behaviours and other psychiatric symptoms to deep brain stimulation.

PD symptoms can be broadly divided between motor and non-motor symptoms. Later, dopamine therapy-related symptoms can also become prominent (Maier et al., 2014). That said, PD patients usually present with motor symptoms. They will, therefore, be discussed here first. The main diagnostic features of PD are **T**remor, **R**igidity, **A**kinesia (or bradykinesia) and **P**ostural instability (TRAP) (Hausdorff, 2009). Other characteristic features of PD include a stooped posture and motor freezing (Jankovic, 2008).

However, as shown in *Table 1*, the most common and diagnostic clinical feature of PD is the slowness of initiation of voluntary movement, i.e., bradykinesia, which must be accompanied by one of muscular rigidity, resting tremor, and an unexplained postural instability (Hughes, Daniel, Kilford, & Lees, 1992). Bradykinesia or hypokinesia can also lead to hypomimia

(emotionless face) and micrographia (small and cramped handwriting) (Shukla et al., 2012). Resting tremors in PD primarily affect the limbs. The most common type of tremor involves a circular movement at the interface of the patient's thumb and index finger, giving it the name 'pill-rolling tremor' (Sveinbjornsdottir, 2016). Furthermore, patients with PD commonly experience gait disorders, including shuffling, blocking and festination. The last two symptoms are more common in the later stages of the disease (Hausdorff, 2009). All motor symptoms are more likely to start unilaterally and progress over the years to become bilateral, albeit with a persistent asymmetry (Marinus & van Hilten, 2015). This asymmetric and unilateral onset of motor symptoms, in addition to clinical response to levodopa and treatment-induced dyskinesia, are considered to be of many supportive diagnostic features according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria, *Table 1*.

PD may also be classified based on the age of onset, with early-onset PD occurring before age 50 and late-onset PD occurring after age 50. That said, some sources have considered different ages to be cutoff for early- and late-onset. Age below 45(Špica et al., 2013), 40 (Schrag et al., 1998) and 55 (Camerucci et al., 2021) are variably used as a cutoff to distinguish early- and late-onset. Nevertheless, in the CRISP study and the current thesis, age below and above 50 is considered a cutoff for early- and late-onset as the former group has shown more motor complications, which is the main indication for DBS therapy (Camerucci et al., 2021; Krause et al., 2022; Schrag & Schott, 2006). In a cross-sectional study involving 208 patients with early onset (mean age = 40) and late-onset (mean age = 62) PD, the authors found that the latter group had significantly more motor and non-motor symptoms, except for restless legs and sweating.

On the other hand, young-onset PD was reported to be associated with more levodopa-induced dystonia and off-time frequency but fewer hallucinations and depression (Špica et al., 2013). A young-onset PD has clinical features that differ from a late-onset PD, such as a slower progressive nature, more common painful dystonia, and less cognitive decline (Bozi & Bhatia, 2003). An essential aspect of very young-onset PD is that there is an increased likelihood of a positive family history of PD. In addition, it is reported that approximately 50% of these cases have a Parkin mutation, a rate that drops to 3% when PD onset is above 30 (Schrag & Schott, 2006). The risk factor section will cover this subject in more detail.

Table 1 UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

Step 1 *Diagnosis of Parkinsonian syndrome*

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive action

And at least one of the following

-Muscular rigidity

- 4-6 Hz rest tremor

-Postural instability not caused by primary visual, vestibular, cerebellar or proprioception dysfunction

Step 2 *Exclusion criteria for Parkinson's disease*

History of repeated strokes with the stepwise progression of parkinsonian features

History of repeated head injury

History of definite encephalitis

Oculogyric crises

Neuroleptic treatment at the onset of symptoms

More than one affected relative

Sustained remission

Strictly unilateral features after 3 years

Cerebellar signs

Early severe autonomic involvement

Early severe dementia with disturbances of memory, language, and praxis

Babinski sign

Presence of cerebral tumour or communicating hydrocephalus on CT-Scan

Negative response to large doses of levodopa (if malabsorption excluded)

MPTP exposure

Step 3 *Supportive prospective positive criteria for Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease)*

Unilateral onset
Rest tremor present
Progressive disorder
Persistent Asymmetry affecting the side of onset more
Excellent response (70-100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
The clinical course of 10 years or more

1.1.1 Prevalence of Parkinson's Disease

The idea that PD is exclusively associated with old age is no longer accepted because 25% of patients present before age 65 (Delamarre & Meissner, 2017). However, the incidence of age-rated PD is increasing in both genders, particularly among males in their 60s and 70s, as revealed by a meta-analysis (Hirsch et al., 2016). The heterogeneity of reported rates of PD prevalence and incidence[2] across studies is due to different inclusion principles and variations in diagnostic criteria. The UK Brain Bank (Hughes, Daniel, Kilford, Lees, et al., 1992), EUROPARKINSON (Breteler et al., 1997), and National Institute of Neurological Disorders and Stroke diagnostic criteria (Gordon et al., 2016) are the most frequently used. A meta-analysis reported that PD prevalence was higher among all the included Chinese studies when UK brain bank diagnostic criteria were used (Chen et al., 2015). The methodologies used by PD epidemiological studies are thought to be another reason behind the heterogeneity in results. In a meta-analysis, the authors reported a higher incidence of PD in the over-80s age group in studies where a door-to-door or mail survey was conducted, compared with studies using administrative records and hospital data (Chen et al., 2001). Hospital registration data does not include patients who are not seeking medical help. Therefore, the use of a mixed methodology would be ideal. Another narrative review, which reviewed worldwide studies, reported prevalence estimates of PD across all ages (40 to above 80) between 41/100,000 and

[2] Prevalence refers to the proportion of people who suffer from an illness at one time or another, whereas incidence indicates the proportion or rate of people who develop a condition within a given period.

1903/100,000 (Pringsheim et al., 2014). The prevalence of PD was found to increase significantly with age by both reviews. However, another study by von Campenhausen et al. reported that the prevalence of PD dropped after 70-80 years old among 39 European studies (Von Campenhausen et al., 2005). Despite the extreme heterogeneity in the available data, conservative estimates consider the prevalence of PD to be around 1-2 cases per 1000 people, 1% of people aged above 60, and 4% in age above 80 group (Tysnes, 2017). In a meta-analysis of PD epidemiology research in Latin America, the incidence of PD was lower in females compared to males when adjusted for age (Llibre-Guerra et al., 2022). The overall incidence rate of PD among females aged ≥ 40 was 37 per 100,000 person-years, whereas among males aged ≥ 40, it was 67 per 100,000 (Llibre-Guerra et al., 2022).

There are concerns about the rising prevalence of PD worldwide. Not only is it a debilitating disease for affected individuals, but its lasting span over decades exceeds any other neurodegenerative disease (Kumar et al., 2022). In addition, the prevalence of PD is rising with an improvement in socioeconomic indicators. This rise also has a modest association with an increase in Gross Domestic Product (GDP), a measure of the economic power of countries (Dorsey et al., 2018). Therefore, PD places an enormous, long-lasting burden on individuals and carers' quality of life and health systems (Obeso et al., 2017; Schapira et al., 2017). When age-standardized analyses are performed, the increase in prevalence may not be solely explained by the rise in the elderly population (Van Oostrom et al., 2016). The decline in tobacco use over the past century in industrialized countries is considered a potential factor in increasing the prevalence of PD. The reason behind this is the correlation between young death and smoking, on the one hand, and PD's link with longevity on the other (Savica et al., 2016). Notably, it has also been demonstrated that tobacco components may have neuroprotective potential, but most of these studies were conducted *in vitro* only (Delamarre & Meissner, 2017).

Moreover, increased caffeine consumption is reported to have a protective effect against dopamine neurodegeneration by antagonizing specific adenosine receptors in the stratum (Chen et al., 2001; Chen et al., 2001). Despite targeting a group of receptors that indirectly enhance dopamine transmission, caffeine has not shown any significant treatment effect in trials (Ren & Chen, 2020). A meta-analysis of four genome-wide association studies reported that a combination of higher intelligence quotient (IQ) and cognitive function-related single nucleotide polymorphisms (SNPs) was associated with a higher risk of PD among males (Odd Ratios=1.3). While it is not yet clear, the current literature suggests a multifactorial model may

be required to explain the increase in the prevalence of PD. The risk factor section will cover this subject in more detail.

1.1.2 Pathology

The pathology of Parkinson's disease is defined by the degeneration and loss of dopaminergic neurons in the substantia nigra (SN) and the accumulation of Lewy bodies in the neurons (Beitz, 2014). This pathological process begins decades before the first motor symptoms emerge (Delic et al., 2020). The underlying pathology of PD can be classified into macroscopical and microscopical pathology. Macroscopically, PD shares features with progressive supranuclear palsy and multiple system atrophy, which similarly cause parkinsonism. One such shared feature is the discolouration of SN in transverse sections of the midbrain and pons (Dickson, 2012). The latter two diseases also show atrophy and discolouration in other regions, which are absent or unremarkable in PD. In idiopathic PD, the brain does not show characteristic features on structural imaging, although there may be mild atrophy of frontal regions and occasionally, ventricular dilation (Saeed et al., 2020). Other studies have reported volumetric reductions in the olfactory bulb compared to cases of multiple system atrophy and healthy controls (S. Chen et al., 2014).

Furthermore, PD patients with non-motor symptoms have shown more extensive grey matter atrophy in cortical and subcortical regions (S. Y. Lee et al., 2018). However, the most consistent finding in PD is neuronal loss in the substantial nigra pars compacta and locus coeruleus (Dickson, 2012). Although conventional magnetic resonance imaging (MRI) generally does not reveal marked structural changes, neuroimaging studies have revealed that PD pathology involves brainstem and subcortical regions at early stages and later progresses into cortical areas (Saeed et al., 2020).

The dopaminergic loss of a specific population of neurons is a common feature of neurodegenerative diseases that cause parkinsonism. The most affected neurons that cause parkinsonism are the dopaminergic neurons in SN that project into putamen. Microscopically, in all neurodegenerative causes of parkinsonism, SN shows neuronal loss, extraneuronal neuromelanin pigments, and gliosis (Hall et al., 2014). Dopamine loss disrupts striatal circuit functions and disparity of the direct and indirect pathways across the basal ganglia (Ashkan et al., 2017), causing motor and cognitive dysfunction (Calabresi et al., 2014). The characteristic histological feature of PD is the appearance of cytoplasmic inclusions called Lewy bodies. Lewy bodies are found in the soma of involved neurons (Sveinbjornsdottir, 2016). Lewy bodies

spread from the medulla oblongata/pontine tegmentum and olfactory bulb predictably within the nervous system. This progression is well described in the Braak staging system of 6 neuropathological stages of PD progression (Braak et al., 2004). It is now clear that α - synuclein oligomers or fibrils play a vital role in the progression of PD (Elsworth, 2020). However, the cause of abnormal processing or clearance that leads to their deposition in Lewy bodies is unclear (Braak et al., 2004). Besides the accumulation of intraneuronal inclusions, multiple mechanisms and pathway dysfunctions contribute to the pathogenesis of PD, including neuroinflammation, defective mitochondria, chronic calcium dysregulation, oxidative stress, and other neurotransmitter system deficits (Zaman et al., 2021). Of note, Lewy bodies and other inclusions, such as Tau proteins, are broadly used to classify neurodegenerative disorders into tauopathies and α-synucleinopathies. PD is not the only neurodegenerative disorder that is classified under α-synucleinopathies diseases. Multiple system atrophy also shows Lewy bodies and Lewy neuritis. However, in the latter, Lewy bodies appear smaller than other components in the affected neurons and are not confined to SN (Dickson, 2012).

For a long time, Alzheimer's disease (AD) and PD have been considered separate neurodegenerative disorders. However, the existence of Lewy body pathology in AD and pathological tau aggregation in PD suggests that these two disorders share some pathological similarities (Erkkinen et al., 2018). Specifically, it seems that α-synuclein, phosphorylated tau protein, amyloid beta, and other proteins interact with the underlying pathological processes (Dugger & Dickson, 2017). In addition, the role these microscopical inclusions play in the pathology is not clear yet. They may have a pathological role or a protective role. For example, the neuromelanin found in Lewy bodies is thought to be a product of the metabolism of dopamine in the cytoplasm. Its increased presence in Lewy bodies is attributed to monoamine vesicular transporter activity reduction. These transporters regulate the rate of metabolism of dopamine inside neurons. Therefore, neuromelanin production is increased when they are inactive, leading to iron chelation and neurotoxicity through increased oxidative stress and the activation of endogenous toxins (Gonzalez-Sepulveda et al., 2023).

1.1.3 Risk Factors

The topic of risk factors for PD has been extensively studied, with some clear but also conflicting and casual findings. PD is among a broad range of complex polygenic disorders that are influenced by the interaction of genetic and non-genetic factors. As with many diseases, the environment and genes are believed to play distinct and overlapping roles in PD (Andrew

et al., 2021). An example of such overlapping is when a less active cytochrome P450 enzyme, CYP2D6, makes some individuals more susceptible to certain toxins. The liver and certain parts of the nervous system, including the SN, are where the enzyme-encoding CYP2D6 genes are expressed (Miksys et al., 2002). Individuals with less active CYP2D6 genes are termed poor metabolizers because CYP2D6 is pivotal in metabolizing environmental toxins and medications. Therefore, these individuals are thought to be more prone to environmental toxins linked to PD (ur Rasheed et al., 2017).

Furthermore, it is estimated that only a small number of PD cases can be attributed to a known genetic component. Therefore, it is accepted that environmental factors play the most significant role in most patients (Chen & Ritz, 2018). Although, the link is not well understood. The environmental hypothesis for the development of PD gained momentum after a group of researchers witnessed that the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in monkeys produced symptoms like the PD in humans, with significant damage to dopaminergic neurons in the SN area (Samuel M. Goldman, 2014). That said, identifying specific environmental factors remains challenging in the pathology of PD due to their instability across cohorts and periods. To illustrate, several pesticides have been suggested to cause the rise in PD cases after World War II (Kenborg et al., 2012). In addition, earlier in 1918, encephalitis-induced parkinsonism was strongly linked to a pandemic influenza virus (Hoffman & Vilensky, 2017). A more recent longitudinal study of two cohorts (n=242 for over 5 years and n=259 for 2.7 years) linked certain pesticides like copper sulphate and dimethylamine salt with a faster disease progression with hazard ratios of 1.36 and 1.73, respectively (S. Li et al., 2023). However, the studies of such risk factors are not always replicated or can present contradictory findings.

Another well-studied risk factor is head injuries, cited in James Parkinson's original essay and by others who followed him (Line Kenborg et al., 2015). Evidence for an association between head injury and PD has been reproduced repeatedly. Parkinsonism may be a consequence of neuroinflammation following head injury, changes in the blood-brain barrier, and other pathophysiological changes (Gao et al., 2015). One study found that having a history of physical activity did not increase the risk of PD when there was no history of head injury. Consistently, regular, vigorous, and routine physical activities have been reported to reduce the risk of PD (Jafari et al., 2013). In addition, a meta-analysis indicates that PD is more likely to be associated with head injuries that cause amnesia or loss of consciousness (Delic et al., 2020). The age at which head injury occurs is also crucial. A retrospective analysis of 507 PD cases

and a 1307 matched control group showed that the association of head injury and PD had a more significant odds ratio when it occurred before age 30 (Gao et al., 2015). Of note, other factors can lead to false associations between a history of head trauma and PD. Falling due to a prodromal gait imbalance, for instance, can also increase the risk of head trauma (Andrew et al., 2021).

On the other hand, a case-control study found that head trauma and PD were not linked in 1705 participants in Denmark (Line Kenborg et al., 2015). This absence of an association between PD and head injury raises questions about the strength of the relationship, but it does not necessarily rule it out. It also indicates different risk factors for PD development across cultures, such as frequency and type of physical activity and various lifestyles (Abbas et al., 2018).

Similarly, engaging in hobbies or jobs that expose one to lead can increase the risk of PD. According to the authors of the retrospective analysis of two genome-wide association study (GWAS) studies of a large cohort, PD was significantly association with accumulative tibia bone-lead measurements (Paul et al., 2021). In addition, to study the effect of different lifestyles on PD risks, a nationwide population-based study selected over 500,000 Korean healthcare users screened at least 3 times during the study. The authors reported that of all selected participants, 2666 patients were diagnosed with PD within 12 years (Yoon et al., 2022). The authors noted that smoking, drinking alcohol, and regular exercise were found to be inversely associated with PD risk. Drinking alcohol was more consistently associated with reduced PD risk in males than females. Females demonstrated a more consistent link between regular physical exercise and a decreased risk of PD, which increased with the intensity of the activity (Yoon et al., 2022). These associations were dose-dependent among an Italian cohort (n=5462). However, in a multivariate analysis, the association did not reach significance (Baldereschi et al., 2003). Such findings may lead us to draw direct connections between PD and some controversial factors, such as drinking and smoking. The consensus among researchers is that more research is necessary to fully comprehend potential confounding factors that could increase the tendency of PD patients to smoke or drink. Yoon et al. (2022) reported that such associations disappeared once the number of regular screenings was controlled for.

The authors noted that in individuals who did not regularly visit doctors, they did not find a link between tobacco and alcohol use behaviour and reduced PD development (Yoon et al., 2022). Another possibility is that the associations result from an interaction between genetic

and environmental factors. CYP2D6, as discussed earlier, has a protective role against neurotoxins. Chronic nicotine exposure leads to this enzyme becoming activated in the SN and increases the neutralization of neurotoxins (Mann et al., 2008). In addition, caffeine has been shown to play a neuroprotective role in mice (Chen et al., 2001) and to reduce the risk of PD in humans in two meta-analyses (Hernán et al., 2002; Noyce et al., 2012). However, like smoking, caffeine risk differs across genders. One reason for this could be that when females receive hormone therapy replacement (oestrogen), caffeine metabolism is inhibited (Ascherio et al., 2004).

There are multiple reasons why these controversial findings can be criticised. Study design is one of them, precisely the issue of case-control *vs* longitudinal studies. Case-control studies can recruit a larger cohort more readily and are more cost-effective. However, retrospective data makes them more susceptible to bias, resulting in less reliable outcomes (Susan Lewallen & Paul Courtright, 1998). It has also been argued that in many of these studies, the number of visits or follow-ups is too low compared to the study's length. The low follow-up rates may lead to biased estimates of outcomes in longitudinal studies (Vincent et al., 2012). In addition, ethnic diversity is not always present in the cohorts of these studies (Mappin-Kasirer et al., 2020). Finally, most of these studies did not investigate other potential confounding variables, such as socioeconomic conditions or comorbidities (Delamarre & Meissner, 2017; Yoon et al., 2022).

On the other hand, the genetics of PD have been extensively studied. In the rare situations when multiple members of one family were diagnosed with PD, the aetiology was found to be monogenic, caused by one highly penetrant genetic mutation. Even though this scenario is uncommon, it led researchers to emphasize the importance of genetic factors as risk factors for PD (Billingsley et al., 2018). Researchers use genome-wide association studies (GWAS) to study the genetic risks of PD, gain a better understanding of the underlying pathology and eventually achieve translational advances in potential prevention and treatments (Billingsley et al., 2018). As a result, numerous genes have been identified to play a significant role in the pathology of the disease. However, genetic risk factors are best known to be responsible for early-onset PD, which comprise a very small proportion of all cases. Two distinct viewpoints offer a profound understanding of the genetic contribution in the genetic side of the debate on risks for PD: the common disease common variant and the common disease rare variant hypotheses (Billingsley et al., 2018). The former asserts that many common variants have a negligible effect that eventually accumulates to cause a significant risk. According to the latter,

rare genetic variants with variable effect sizes impose a relatively significant risk (Aborageh et al., 2022).

Risk genes identified include but are not limited to Synuclein Alpha (SNCA), Leucine-rich repeat kinase 2 (LRRK2), glucocerebrosidase (GBA), and microtubule-associated protein tau (MAPT). Some genetic loci that have been found to cause monogenic PD, such as SNCA, may contain mutations that carry a lower risk of PD; therefore, they are known to be pleomorphic (Billingsley et al., 2018). Simply put, different mutations could cause progressive autosomal dominant early-onset PD or only slightly increase risk. Another important pleomorphic locus is LRRK2. According to multiple studies, people who have inherited LRRK2 have a 29% risk of developing PD before age 60 and 75% after age 80. South European, North African Arab, Middle Eastern and Jewish populations have a higher prevalence of this variant (Ben-Joseph et al., 2020). Despite the extensive genetic research and valuable findings, only 6-7% of the PD burden is known to be associated with identified loci, and the heritability of PD is not higher than 27% (Schrag & Schott, 2006). Therefore, more research is needed to understand the disease's genetics fully. The objective of ongoing and future research will be to identify all risk loci and understand their relationship with environmental risk factors and the underlying pathology of PD.

1.1.4 Non-Motor Symptoms of Parkinson's Disease

Even though the initial diagnosis and treatment plan for PD is based on motor symptoms, the generally poorly treated non-motor symptoms of PD have a debilitating burden and clinical significance (Sauerbier et al., 2016). As illustrated in *Figure 1*, the most prevalent non-motor symptoms of PD include rapid eye movement, REM-related sleep disorders, psychiatric disorders such as cognitive impairment, depression and anxiety, dysosmia and constipation with a prevalence of 33-46% (Mahmood et al., 2020), 35% and 60% (Han et al., 2018), 40% (Fang et al., 2020) 46-97% (Lin et al., 2022) and 66% (Pedrosa Carrasco et al., 2018), respectively. A meta-analysis of studies that collected self-reported data retrospectively from PD patients found that compared to a matched control cohort, a group of these non-motor symptoms are often present even before motor symptoms appear and PD is diagnosed, as shown in *Figure 1* (Chen et al., 2015). Non-motor symptoms commonly lead to significant disability, low quality of life and mortality. Population studies have shown that psychiatric symptoms have a significant impact on healthcare costs and are a significant risk factor for admission to nursing homes (Aarsland et al., 1999; Chen, 2017).

The current thesis is devoted to discussing the impact of Deep Brain Stimulation of Subthalamic Nucleus (DBS-STN) on psychiatric symptoms and syndromes: impulsive behaviours, mood symptoms, apathy, psychosis and psychotic symptoms, personality traits, cognitive function, and suicidality. In addition, the research is expanded to examine the burden that carers encounter before and after DBS operations. In the next chapter, the effect of DBS on psychiatric symptoms is systematically reviewed in the current literature. However, in the following section, a brief introduction to psychiatric symptoms of PD is discussed.

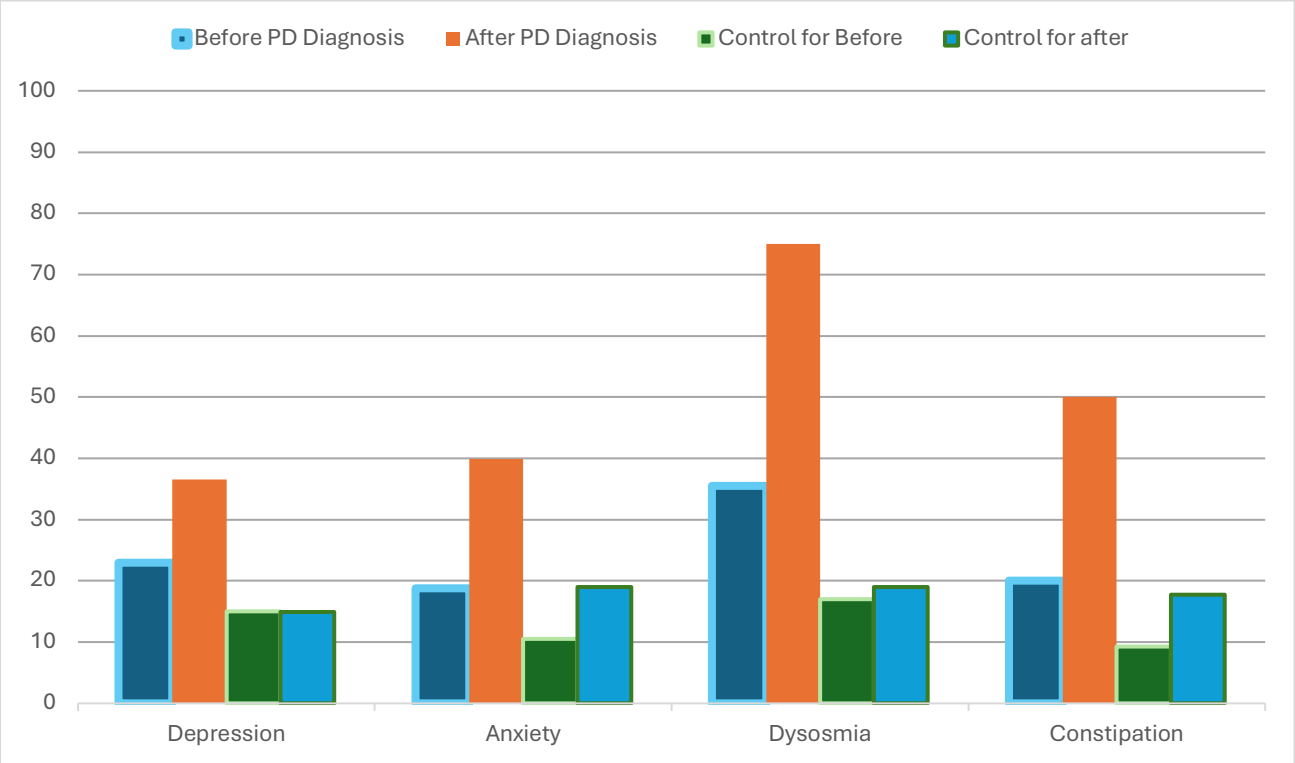


Figure 1 Prevalence of Non-Motor Symptoms Before and After PD Diagnosis

1.1.4.1 Impulsive Behaviours

Impulse Control Disorders (ICDs) are defined as behaviours that are performed repetitively, excessively, and compulsively to the extent that these behaviours interfere negatively with the activities of daily living of patients and their carers (Okai et al., 2011). ICDs, together with other related impulsive and compulsive behaviours, are collectively referred to as Impulsive Compulsive Behaviours (ICBs) (Evans et al, 2019). Therefore, ICBs all share a repetitive, reward, or incentive-base nature. In this thesis, "ICDs" is used when the 4 major ICDs listed below are being referred to, whereas "ICBs" will be used when all impulsive behaviours are being discussed collectively, including ICDs and "other common related impulsive and compulsive behaviours" described below.

There are 4 major ICDs in PD:

1. Pathological gambling
2. Compulsive buying
3. Hypersexuality
4. Binge eating (Weintraub et al., 2010a, 2015)

Other common related impulsive compulsive behaviours in PD include dopamine dysregulation syndrome (DDS) - a drug addiction-like state associated with self-medicating with inappropriately high doses of PD medication, in particular levodopa (Giovannoni et al., 2000), punding - repetitive purposeless behaviours such as collecting or rearranging objects (Evans et al., 2004), hobbyism - similar but higher level than punding such as excessive artwork and hoarding - the acquisition of and failure to discard objects (O'Sullivan et al., 2010). In recent years, there has been increasing evidence and awareness regarding the frequency of ICBs in PD. ICBs are often unreported by patients and unrecognized in routine assessments. Consequently, unnoticed ICBs can have a catastrophic deleterious effect on patients' and carers' financial, social and relationship status over time (Papay et al., 2011). A study of 3,090 PD patients in North America found a prevalence of severe ICBs in 13.6% of PD patients, which is high when compared to the background population rate of around 5%. More recently, in a multicentre longitudinal cohort study in PD patients (n=411), after 5 years of follow-up, the prevalence of ICBs among the cohort increased from 19.7% at baseline to 32.8% (Corvol et al., 2018). Reportedly, a very high percentage of patients without a formal ICB diagnosis can test positive on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) (Evans et al, 2019), but this is not sufficient to assess ICBs in routine clinical care (Weintraub et al., 2015). To elaborate, the QUIP is a screening tool that screens only for urges or thoughts about an impulsive behaviour rather than executing that behaviour. The former has been linked to the dorsal striatum, whereas the latter has been linked to the ventral striatum (Lawrence et al., 2003). A semi-structured interview, like the Parkinson's Impulse Control Scale (PICS) and a severity rating questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS), provides more detail by investigating beyond the urge and assessing the severity and social impacts of impulsive behaviours themselves.

ICBs are strongly associated with DA use (V. et al., 2011; Weintraub et al., 2010). Independent associations are reported between the lifetime average DA daily dose and duration of treatment

with ICB severity (Corvol et al., 2018; Weintraub et al., 2015). Other factors associated with ICBs include:

1. Younger age; male sex; early-onset PD; being unmarried; current cigarette smoking; a personal or family history of gambling or alcoholism; impulsive or novelty-seeking traits (Voon et al., 2011; Weintraub et al., 2015).
2. Several psychiatric symptoms are more common in PD patients with ICB, including anxiety, depression, and sleep disturbance (Leroi et al., 2012; Weintraub et al., 2015).
3. The incidence of ICBs in untreated PD is very similar to controls; therefore, ICBs are considered to be a side effect of treatment, in particular dopamine agonist treatment, rather than a manifestation of PD *per se* (Weintraub et al., 2010).
4. ICBs in PD are associated with decreased quality of life (Phu et al., 2014).
5. ICBs are frequently seen in DBS clinics (16 %) because patients being considered for DBS typically have tried high-dose medication, are younger and may be more likely to be seeking high levels of quality-of-life improvements (Pondal et al., 2013; Samuel et al., 2015).

Few published studies statistically analysed the factors that might predict changes in ICBs following DBS (Doshi & Bhargava, 2008.; Eusebio et al., 2013.; Lim et al., 2009; Polosan et al., 1843; Scherrer et al., 2020; Smeding et al., 2007; Zahodne et al., 2011). The lack of consistent evidence means that at present, DBS clinicians are not clear on precisely how to counsel patients as to whether DBS could improve or worsen ICBs when they co-exist with motor fluctuations/dyskinesias (which are the indications for DBS), as they commonly do (Eusebio et al., 2013; Shotbolt et al., 2012). This multicentre observational study will be a pragmatic "real-world" study to evaluate symptoms of ICBs and other neuropsychological aspects, including mood, quality of life, personality, social activity, etc., in detail before and after DBS, identifying factors that are important in predicting or determining whether ICBs will improve or worsen post DBS. This study will help clinicians answer this question directly by measuring ICBs and correlating them to the factors mentioned below, leading to improved patient counselling in movement disorder clinics.

1.1.4.1.1 Impulsivity, Parkinson's Disease and the STN Role

Like addictive behaviours, impulsive behaviours are thought to be a result of abnormalities of the neuroanatomical substrate linked to motivational behaviours and reward processing (Eisinger et al., 2022). However, among PD, these behaviours have clearer pathophysiology. Focusing on central symptoms is deemed the best course of action to understand risk factors and manage such behaviours in light of underlying pathology in PD (Okai et al., 2011). The main reason is to avoid being overwhelmed by aetiology and classification schemes, which negatively affect clinical care. The central symptom of impulsive behaviours in PD is a lack of decision-making or a preference for immediate rewards while being aware of the potential negative consequences (Averbeck et al., 2014).

Moreover, while understanding the immediate satisfaction that comes with impulsivity is important, it is also important to understand its physiological or pathological precursors. In the CRISP study, in addition to two validated impulsivity scales, the negative urgency will be assessed alongside other personality traits related to impulsivity by using the Urgency, Premeditation, Perseverance, Sensation seeking and Positive urgency Impulsive Behaviour Scale (UPPS-P). Negative urgency is a term used to describe a tendency to exhibit impulsive behaviour when distressed. This group of behaviours has difficulty avoiding repeated actions in common (Okai et al., 2011). Besides the behaviours that are prevalent in PD, which are discussed here, there are others, such as substance abuse, aggression, or non-suicidal self-harm (Bresin et al., 2013).

Negative urgency is not only a personality trait (as is often theorised) but also a modifiable variable targeted in treating ICBs. Of note, not everyone with negative urgency presents with impulsivity. Therefore, it can be regarded as one of the potential outcomes of being distressed. Indeed, negative urgency has also been associated with suicidality (Anestis & Joiner, 2011). Whether it is an inherited trait or an outcome of an impaired coping mechanism in stressful situations, it provides a perspective into the problematic behaviours. To illustrate, negative urgency was simultaneously predictive of alcohol dependence symptoms, the prevalence of drinking problems and smoker status among pre-adolescents, and violence, unprotected sex and antisocial behaviour in college students in multiple studies (Conner et al., 2009; Fischer et al., 2007; Settles et al., 2012; Trobst et al., 2002). In the current context, negative urgency and its pathophysiology can help understand impulsive behaviours. Pathophysiologically, negative urgency is related to the activation of the sympathetic nervous system. An experimental study of 205 psychology students reported that increased resting sympathetic nervous activity was

associated with increased emotional impulsive activities (Peters et al., 2018). Of Interest, DBS-STN has been shown to activate the sympathetic autonomic nervous system, which is directly linked to negative urgency (Basiago & Binder, 2016). Although this effect can improve other stress-related symptoms, it can also increase amygdala activity and induce poorer executive functioning under stress (Pagen et al., 2021).

To understand the role of STN in impulsivity, it has to be reiterated that from a cognitive point of view, impulsivity is considered a motivation-based product of abnormal reward processing. To further illustrate, a particular reward for a certain action is abnormally processed, and impulsivity, as a motivational product of such abnormal processing, is the outcome observed in the form of repeated, difficult-to-control and maladaptive behaviours. Both DBS targets in PD, STN, and internal globus pallidus (GPi) are known to be important structures linked to the process (Eisinger et al., 2020, 2022). The precise role STN plays in impulsivity is not yet understood. However, STN stimulation increases risky decision-making and reduces inhibitory force. Compared to GPi, STN does not have separate motor and reward circuit anatomy, making it more difficult to avoid worsening impulsivity after DBS (Eisinger et al., 2022). In addition, the two structures are thought to have distinct associations with impulsivity. On the one hand, GPi is thought to be involved with reward expectation, while STN can inhibit an impulse until it has been processed and has passed cognitive evaluation (Rossi et al., 2017).

Future studies aim to find the correct local field potential or oscillatory activities in STN to avoid such adverse events, which may negate post-DBS DA-reduction-related improvements in impulsivity (Pearson et al., 2017). In addition to personality traits and PD-related disturbances in reward processing, dopaminergic agents are also known to increase the risk of impulsive behaviours. For example, Pramipexole and Ropinirole are shown in multiple studies to increase the risk of various impulsive behaviours (Garcia-Ruiz et al., 2014; Weintraub et al., 2006). It is believed that such an effect results from their higher affinity toward D3 dopamine receptors than D2 dopamine receptors (Zhang et al., 2021). Other medications used in the treatment of PD, such as levodopa (Weintraub et al., 2010) and monoamine oxidase inhibitors (Samuel et al., 2015), have also been linked to impulsive behaviours in PD. However, the risk for all antiparkinsonian medications to induce impulsive behaviours is reported to depend on their dosage and course on one hand and patients' impulsive personality traits, age and gender on the other hand (Okai et al., 2011).

1.1.4.2 Mood Symptoms

PD patients have a high prevalence of mood symptoms. This is partly attributed to the involvement of noradrenergic, dopaminergic, and serotonergic neurons in underlying pathology in PD and, consequently, impairment of the limbic-cortico-striato-thalamocortical circuits, which play a parallel role to the fear circuit in the brain (Carey et al., 2021; Thobois et al., 2017). Depression also correlates with the degree of substantia nigra (SN) and raphe nuclei anatomical changes (Walter et al., 2007). The latter is the origin of serotonin release, a neurotransmitter that plays an essential role in mood regulation (Santiago, 2016). However, others have not found such relations between neuroanatomical and neurofunctional changes in neuroimaging studies (Wen et al., 2016). This may be due to the failure to control the effects of antidepressants before and during the study. In general, the evidence for depression being a common pathology in PD is robust (Aarsland et al., 2012; Cuijpers et al., 2010; Fiske et al., 2009; Frenklach, 2016; Koerts et al., 2008; Lawrence et al., 2014; Pusswald et al., 2019; Schrag et al., 2007; Wen et al., 2016).

Although the prevalence of a diagnosis of depression in early stages of PD is reported at 17%, almost half of the PD patients exhibit symptoms in later stages (Koerts et al., 2008; Reijnders et al., 2008; Wen et al., 2016). Depression is believed to be a prodromal symptom rather than a risk factor for developing PD. This was supported by the results of a study of a recently diagnosed (within 3 years) PD cohort (n=371), who were compared to a healthy matched population and their non-PD siblings. The authors reported that in their cohort, a diagnosis of depression frequently preceded the PD diagnosis (Jacob et al., 2010). Precedented symptoms of depression may not always be linked to a diagnosis of a depressive disorder, as individual symptoms may be a consequence of the underlying pathology of PD, which includes dopaminergic and serotonergic neurodegeneration (Aarsland et al., 2012). For example, anhedonia, which is among the key features of depression, may precede depression and motor symptoms and occurs in Parkinson's patients who are not depressed. It is believed that this is due to the damage caused to the reward system by the degeneration of dopaminergic neurons in the mesolimbic pathway (Stocchi et al., 2023). The pathological neuroinflammation underlying PD is also believed to cause changes in the serotonergic system, which is more closely related to depressive mood, by changing the metabolism of tryptophan (Santiago, 2016). Other risk factors for the development of depression are reported to be gender (female), early onset of motor symptoms (before age 40) and cognitive impairment (Noyce et al., 2012). Socioeconomic and chronic medical conditions are also reported to be risk factors for

depression in PD (Aarsland et al., 2012; Frenklach, 2016; Koerts et al., 2008). That said, it can be demonstrated that neurobiological factors are more influential than psychosocial ones, as depression symptoms are present 4-6 years before a PD diagnosis is established (Ishihara & Brayne, 2006). In addition, the α-synuclein accumulation and consequent neurodegeneration start in non-dopaminergic brainstem regions such as locus coeruleus and raphe nucleus, according to Braak staging system (Braak et al., 2003).

The diagnosis of depression remains challenging and may lead to misdiagnosis. This is because of overlapping symptoms of mood disorders and their core symptoms with those of PD. For example, loss of facial expression, loss of appetite and sleep disturbance are common in PD without depression (Aarsland et al., 2012). Hence, the standard clinical interview using the Diagnostic and Statistical Manual-5 (DSM-5) criteria for diagnosing mood disorders in PD remains the gold standard. A proper diagnosis of depression and assessment of its severity is essential because other various conditions may be attributed to depression symptoms in the same age group, such as vascular disease or thyroid disease or side effects of some medications, including beta blockers (Fiske et al., 2009).

Furthermore, major depressive disorder may carry a potential prognostic significance for decline in cognition (Pigott et al., 2015). By addressing depression early in PD, it can lessen its negative impact on prognosis, burden, and social life (Frenklach, 2016). Pharmacological treatment can also be challenging due to reduced efficacy and increased side effects in PD patients (Pusswald et al., 2019). Furthermore, reducing motor symptoms either via antiparkinsonian medications or alternative, invasive treatments like DBS can increase patients' capability to engage in more social interactions and movement exercises that are shown to help reduce depression symptoms (Koerts et al., 2008). In this thesis, there is more discussion about the effects of STN-DBS on depression. Anxiety is also reported at a higher rate (31%) in PD patients compared to the rest of the population (Carey et al., 2021). This may include social phobia, specific phobia, general anxiety disorder or panic disorders (Leentjens et al., 2011). Just like depression, anxiety disorders may have symptoms that overlap with other conditions, such as other mood disorders, sleep disorders and fatigue, which are often present in PD. The severity of anxiety is reported by a systematic review of neuroimaging studies to be associated with reduced cortical metabolism in the orbitofrontal cortex, dorsolateral prefrontal cortex, ventrolateral PFC, and the cingulate cortex as well as reduced striatal metabolism (Carey et al., 2021; Thobois et al., 2017). These cortices are thought to play a role in the cognitive regulation of emotions. In addition, changes in neural connectivity between

basal ganglia and regions closely linked to mood in the brain, such as the anterior cingulate cortex, are postulated to contribute to the development of anxiety and other mood symptoms (Carey et al., 2021).

Other risk factors for anxiety among PD patients have been identified as age, gender or social-related factors (Chang et al., 2012). Most patients above age 50 are prone to many of these risk factors. Age-related risk factors are medical conditions including, but not limited to, cardiovascular diseases, hypertension, and cognitive impairment (Vink et al., 2008). Furthermore, the severity of PD and its impact on quality of life are strongly linked to anxiety. It is also identified to be one of the aggravating factors for PD (Leentjens et al., 2011). In this circumstance, anxiety can be reduced by reducing the severity of motor and non-motor symptoms of PD. This topic is also further elaborated on in this thesis.

1.1.4.3 Cognitive Dysfunction

In comparison to generally healthy individuals, PD patients have a higher risk of developing dementia (Geurtsen et al., 2014). More than 80% of PD patients will develop dementia, and the remainder meet the criteria for mild cognitive impairment (MCI) (Fang et al., 2020; Pigott et al., 2015). In addition, cognitive impairment is one of the main causes of nursing home placement (Aarsland et al., 1999). An association has been reported between dementia onset, older age and Lewy body scores (Reid et al., 2011). Mild cognitive impairments in executive function, visuospatial impairments and memory domains can be detected as early as the onset of PD; however, deficits in other domains can happen later as the disease progresses (Muslimović et al., 2007). A prospective study of 141 PD patients with normal cognitive function reported that over 6 years, half of their participants suffered from MCI, who developed dementia 5 years after being diagnosed with MCI (Pigott et al., 2015). Early detection and management of MCI is crucial due to its association with other debilitating psychiatric symptoms such as psychosis (Chen, 2018), anxiety (Gallagher & Schrag, 2012) and depression (Prange et al., 2022). Although cognitive impairment is considered one of the most devastating non-motor symptoms of PD, this thesis will only focus on self-reported changes in cognitive function. The reason for this is that participants of the CRISP study are selected for deep brain stimulation therapy for their uncontrolled motor symptoms, for which any patient with moderate to severe cognitive impairment is deemed ineligible. In addition, the primary outcome of the CRISP study is to focus on the clinical response of impulsivity to deep brain stimulation in PD. A descriptive analysis of self-reported cognitive difficulties and any associations that may exist with other outcomes of interest is given.

1.1.4.4 Apathy

Prevalence of apathy among PD has been reported to be as high as 58% using both patient's perception (Gaenslen et al., 2011; Zgaljardic et al., 2007) and validated tools such as the Lille Apathy Rating Scale (LARS) (Barber et al., 2018). Apathy can be the dominant non-motor symptom in a distinct PD phenotype called the Park apathy subtype (Sauerbier et al., 2016). Clinically, subtyping PD based on non-motor symptoms is advantageous because non-motor symptoms can be dominant and have a potential prognostic value. In this subtype, apathy is associated with more severe motor symptoms and cognitive impairment (Heron et al., 2018). Apathy is defined as a behavioural, emotional, and motivational pattern, including a lack of interest in everyday activities and participation in everyday social events, lack of initiative, difficulties in completing activities, indifference, and a flattening of affect (Levy et al., 1998; Pluck & Brown, 2002). Owing to its phenomenology, it has been suggested that apathy should be considered a behavioural problem as patients show reduced self-generative and self-initiated purposeful acts (Dickson & Husain, 2022). However, this proposed framework does not exclude other dimensions like emotion and cognition. Indeed, the scales used commonly in research, such as the Apathy Evaluation Scales (AES), include items that cover all three dimensions (Lueken et al., 2017). In addition, other scales add more newly proposed dimensions, such as social life and personality traits (Jao et al., 2016) and environment (Jao et al., 2016).

Furthermore, it was previously considered a late-stage symptom, primarily in elderly patients. However, according to current literature, apathy is observed at all stages of the disease (De Waele et al., 2022). PD patients reported a significant decrease in travel several years before being diagnosed, according to a prospective study of a large population in the Netherlands. However, the authors did not specify if the reason was confirmed to be a lack of motivation (Darweesh et al., 2017). Furthermore, the clinical manifestations of apathy have some similarities to those of depression and anxiety, such as fatigue, agitation, psychomotor retardation, lack of facial expression, and difficulties in concentration (Wen et al., 2016). Having been reported frequently in PD patients who did not have anxiety and depression, apathy is now considered a separate entity linked, but not limited, to dopaminergic loss in the striatum and basal ganglia. Even though apathy has been assumed to be a hypodopaminergic state, it can coincide with other hyperdopaminergic conditions, such as impulsive disorders (Palmeri et al., 2022), and may not respond to dopaminergic medications (Mele et al., 2020). Therefore, it warrants recognition of a more complex underlying pathology.

To better understand the various clinical phenotypes of apathy, De Waele and colleagues (2022) have subtyped apathy into behavioural, motivational, cognitive and self-awareness with different underlying pathology, neurotransmitters and neural pathways involved (See *Figure 1*). The study of apathy mainly revolves around the drive for goal-directed behaviours, whether its absence is due to an impaired cognitive dysfunction, reduced internal stimuli, reduced emotional response or a decline in self-reflection (Marin, 1991; Le Heron et al., 2018). Although it may seem like a simplification, this approach has been beneficial in linking the primary symptoms of apathy to brain regions and the neurotransmitters that mediate them. Accordingly, apathy is a clinical manifestation of dysfunction in different neural networks between the two regions regulated by specific neurotransmitters (R. Levy & Dubois, 2006). In other words, apathy stems from dysfunctional connectivity between the frontal lobe and the basal ganglia (Santangelo et al., 2013).

Furthermore, distinguishing apathy from other psychiatric diseases, such as depression or cognitive impairment, remains a challenge for clinicians (Martínez-Horta et al., 2014). Patients and relatives may believe that their apathy-related behaviour is associated with their disability rather than a specific complaint, which is why they tend to underreport it (Zgaljardic et al., 2007). Identification of apathy as early as possible in PD is crucial as it is reported to be an indicator of current MCI and has prognostic potential for quality of life and cognitive impairment (Martin et al., 2020).

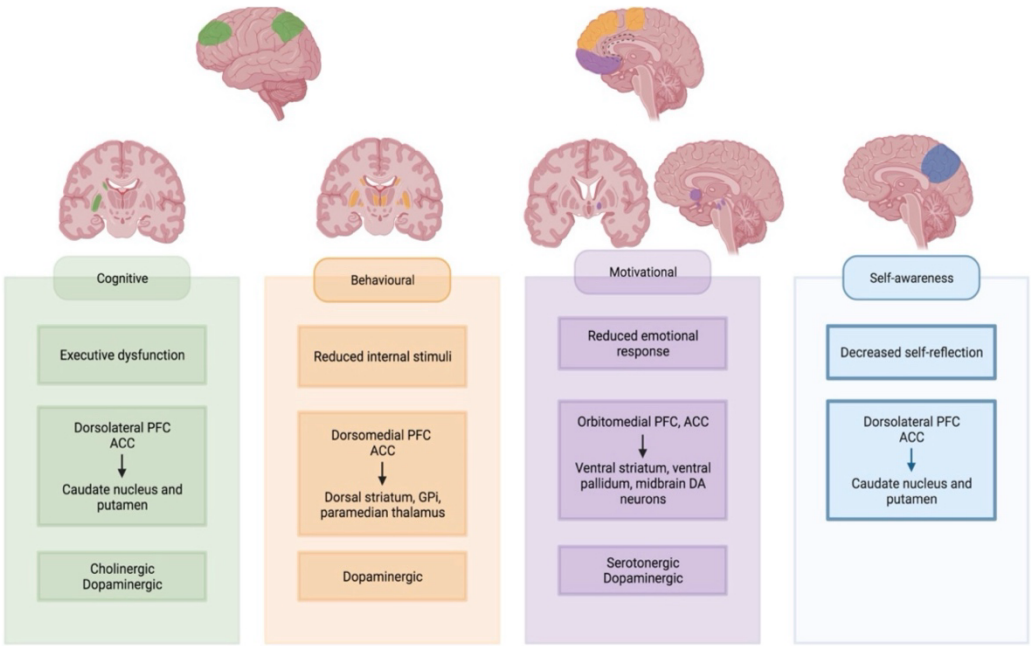


Figure 2 Underlying Neural Networks in Apathy

This figure shows neural networks that are thought to underlie each apathy subtype. In addition, involved cortical regions, basal ganglia and neurotransmitters are shown. Abbreviations: PFC: prefrontal cortex; ACC: anterior cingulate cortex; GPi: internal globus pallidus; DA: dopaminergic.

1.1.4.5 Psychosis

Recurrent and chronic psychotic symptoms are present in 60% of PD cases, and this number rises to 75% when dementia is present (Chen, 2017). PD psychosis is characterized by recurring or persistent symptoms that include at least one of false sensation of presence, illusions, hallucinations, or delusions for at least one month after the onset if other potential causes are excluded (Powell et al., 2020). In PD, hallucinations and delusions are common psychotic symptoms, with the former being much more common (Grover et al., 2015). In general, hallucinations in PD range from non-disturbing visual distortions to well-formed hallucinations, such as an image of a person (Chen, 2017). Moreover, auditory hallucinations are less common than visual hallucinations (Gallagher & Schrag, 2012). Other less disturbing psychotic symptoms of PD include feeling the presence of someone behind or near the patient, also known as presence hallucination, or sensing a brief passage of objects, animals, or people in the peripheral visual fields, also known as passage hallucinations (Diederich et al., 2000). With the progression of PD, these symptoms can become disturbing. Therefore, the presence of any psychotic experience requires careful monitoring. As for delusions, they are less common than hallucinations, occurring at a rate of 5-10% among PD patients on antiparkinsonian medications (Holt et al., 2010). The most common delusional theme in PD is persecutory, such as suspicions of others having stolen or intentionally harming them. The presence of psychotic symptoms is associated with depression and a lower quality of life (Chen, 2017). Like hallucinations, delusions present with more distressing and complex themes when concurring with dementia and delirium (Goldman et al., 2011).

The exact pathophysiology of psychosis is not yet known. Old age, comorbid medical conditions such as dementia, depression, Rapid Eye Movement (REM), sleep behaviour disorder, and visual disorders, in addition to PD severity and duration, are reported as nonpharmacologic risk factors for the development of psychosis in PD (Chang & Fox, 2016). Of note, it is thought that minor visual hallucinations with intact insight indicate involvement of the basal nuclei. In contrast, a well-formed multimodal hallucination indicates the progression of the disease to multiple cortical regions (Ffytche et al., 2017). In addition, patients with visual hallucinations are also known to have a higher total Lewy body deposition in addition to a higher Lewy body density in regions involved with executive function and visual processing (Harding et al., 2002; John-Paul Taylor, 2011; Powell et al., 2020). Receiving

PD medication is not necessary for the development of psychosis. However, several medication classes, such as dopamine agonists, amantadine, levodopa, anticholinergics, catechol-O-methyltransferase inhibitors, and monoamine oxidase type B inhibitors, all have been variably linked to the development of psychosis (Goldman et al., 2011).

It was hypothesized that long-term dopaminergic medications cause hypersensitization of D3 and D4 dopamine receptors in the mesolimbic pathway, causing the high prevalence of psychosis (Chou et al., 2005). However, multiple studies challenge the hypothesis that PD psychosis is simply dopaminergic intoxication. These reports failed to find any difference in the daily dose of levodopa between those with and without hallucinations (Fénelon et al., 2000; Sanchez-Ramos et al., 1996). Therefore, the underlying pathology of PD psychosis extends beyond the dopaminergic system. Others found that hallucinations do not occur following the administration of high-dose intravenous levodopa (Goetz et al., 1998). Furthermore, dopamine agonists were only weakly associated with the time to onset of hallucinations in a study of over 400 PD patients (Williams & Lees, 2005). Moreover, as mentioned above, PD-related psychosis is found to be strongly influenced by the intrinsic factors of PD, which include older age, advanced disease, cognitive decline, depression, visual impairment, and even genetic predisposition (Chang & Fox, 2016; Chou et al., 2005; Gallagher & Schrag, 2012; Zhang & Ma, 2022). Nevertheless, a 'drug holiday' from dopaminergic medications was one of the first therapeutic interventions for psychotic symptoms (Koller et al., 1981). Nowadays, that practice is not commonly used, but reducing or eliminating dopaminergic PD medications is a standard approach.

An alternative hypothesis was prompted by the fact that anticholinergic medications can also cause psychosis. In the striatum of patients with PD, where dopaminergic neurons have degenerated, there is a state of compensatory overactivity of acetylcholine function, leading to an imbalance (S. Zhang & Ma, 2022). The use of anticholinergics to treat symptoms attributed to this imbalance can cause psychotic symptoms. Moreover, stopping anticholinergic medications decreases hallucinations, and these medications are commonly the first ones to be stopped in the context of PD psychosis (Sawada et al., 2013). Therefore, clinicians need to be mindful of non-PD medications with anticholinergic properties.

Loss of serotonergic neurons and the effects of dopaminergic medications can also play a role in the development of psychotic symptoms in PD. Abnormalities in the serotonergic system are also linked to sleep and mood disorders in patients with PD (Prange et al., 2022). PD patients with psychosis were found to have higher levels of red nucleus, raphe nucleus, and

globus pallidus serotonin than those without during early autopsy studies (Birkmayer et al., 1974). It is thought that the degeneration involving cortical serotonergic neurons caused by Lewy body deposition leads to the upregulation of serotonin 5-HT_{2A} receptors (Powell et al., 2020). These receptors are reported to be involved in visual hallucination in PD psychosis (Stahl, 2016). Their involvement is supported by others who reported the interaction of hallucinogenic agents with 5-HT_{2A} (Onofrj et al., 2019) and ameliorating effects of Pimavanserin, an inverse agonist of 5-HT_{2A} on psychotic symptoms in PD (Cummings et al., 2014). Of note, despite some conflicting reports (Cancelli et al., 2004), selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors are reportedly safe for PD cohorts (Clinical Commissioning Policy: Deep Brain Stimulation (DBS) In Movement Disorders Prepared by the NHS Commissioning Board Clinical Reference Group for Adult Neurosurgery, 2013; Seppi et al., 2019). Dopamine Replacement Therapy (DRT) is found to not affect the remaining serotonergic neurons in the basal ganglia (Politis & Niccolini, 2015). Dopamine administration may also lead to overstimulation of serotonin receptors, which modulate dopamine neurons in the ventral tegmental area, causing cognitive and behavioural disturbances by excitation of the limbic system and inhibiting the prefrontal cortex (Goldman et al., 2011). Furthermore, in other autopsy studies of PD patients with hallucinations, abnormalities in brain serotonin receptors in multiple regions, including the ventral visual pathway, have been discovered (López-Giménez & González-Maeso, 2018). Based on these findings, it appears that there are changes in the pathways that control visual and cognitive processing, suggesting that serotonin receptor pharmacology plays a role in PD hallucinations.

1.1.4.6 Suicidality

Suicide, a catastrophic event in psychiatric disorders, maintains a steady presence on the list of the top 10 causes of death, even in first-world countries like the USA (Shepard et al., 2019). Elderly and patients with neurological disorders like PD are particularly at risk of suicide (Soulas et al., 2008). It is noteworthy that suicidal thoughts are prevalent among PD patients and can occur in 17-30% of cases; however, there is a lack of literature on completed suicides (W. Li et al., 2018). Neither genetic nor epigenetic causes behind suicidality among PD patients have been investigated in high-quality studies (Shepard et al., 2019). Depression is a well-known risk factor for suicidality in both the general population and the elderly (De Leo, 2022). Clinically significant depression is reported in one-third of PD patients. (Wen et al., 2016). Furthermore, depression in PD tends to phenomenologically differ from that in the general population by presenting with less self-guilt, worthlessness, and melancholy (Kritzinger et al.,

2015). It is still considered a significant risk factor for having suicidal thoughts, behaviours or completing suicide. Of note, suicidal ideation may not lead to completion but serve as a reliable symptom of depression in PD (Y. Y. Chen et al., 2021).

Moreover, psychosis and delusions, in particular, are thought to increase suicide risk (Chang & Fox, 2016). Other psychiatric comorbidities such as anxiety (Doshi et al., 2020), substance abuse (Yoshimasu et al., 2008) and impulsivity (Weintraub et al., 2013) are reportedly associated with increased risk of suicidality. However, it is noteworthy that a profound investigation of the relationship of these variables with suicidality is missing (W. Li et al., 2018). Results of investigations on relationships between cognitive function and suicidality are inconclusive and affected by the fact that many studies exclude cognitively impaired participants (Nazem et al., 2008). Regarding PD as a risk factor, studies of populations of different ethnicities have reported that PD patients have a 2-5 times higher risk for suicide in comparison to a matched healthy group for age and gender (T. Lee et al., 2016; Pritchard & Baldwin, 2002). Although disease severity and duration are weakly associated, suicidality seems to be more commonly coincident with some motor symptoms but not others. Dyskinesia (Boel, Odekerken, Schmand, et al., 2016) and fluctuation of motor symptoms (Koerts et al., 2008) are less commonly associated with suicidality, whereas rigidity, bradykinesia and postural instabilities are correlated (T. Lee et al., 2016; Voon et al., 2008).

As for medications, withdrawal of levodopa or the dopamine withdrawal syndrome is reported to be associated with suicidality (Kwan et al., 2022; W. Li et al., 2018; Shepard et al., 2019). This is seen as one of the reasons why placing patients on a 'drug honeymoon', as covered in the previous section, is less commonly done. Others have investigated the effect of invasive treatments, such as deep brain stimulation of the subthalamic nucleus, on suicidality, which is reviewed in more detail in the results of the narrative review in *Chapter 2* and the results of the CRISP study in *Chapter 5*. The rate of suicidal ideation is much higher than that of attempt or completion (Shepard et al., 2019). It is challenging to measure suicidal ideation because many suicidal patients tend to hide it (Nazem et al., 2008). Of note, for risk factors for suicidality, results radically differ between suicidal ideation and suicidal attempts. For instance, having medical comorbidities increases suicidal ideation, whereas patients who complete suicide have fewer comorbidities (Rezvani et al., 2017). In addition, older PD patients have a higher risk of completing suicide, whereas younger patients have a higher risk for suicidal ideation (Ahmedani et al., 2017). Whether living with suicidal ideation from early years will result in completing suicide later is a subject to be investigated with long-term follow-ups and requires

patients' openness about such ideation. Furthermore, male gender, ethnicity (Caucasian), and living in rural areas are considered risk factors for suicide; however, the role of marriage, employment and education are still not clear (Jeong et al., 2022; W. Li et al., 2018; Myslobodsky et al., 2001).

1.1.5 Current Treatments for Parkinson's Disease

Figure 3 displays different pharmacological approaches for treating symptoms of PD. While the aetiology of PD remains unclear, it is common practice to use a direct approach to manage the disabling and debilitating symptoms. That is to say, to address the primary cause of PD motor dysfunction: the loss of dopaminergic activity in the striatum (Ellis & Fell, 2017). In other words, almost all of the current standard therapies for PD act to increase striatal dopamine levels to alleviate related motor symptoms.

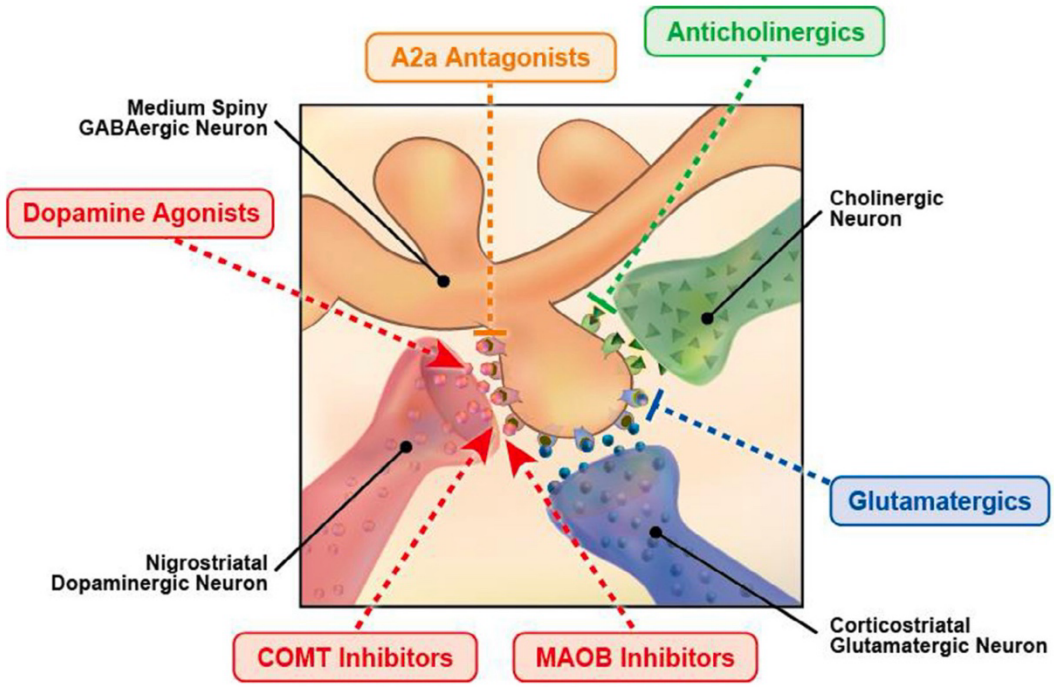


Figure 3 A Diagram Showing Different Approaches to Treating Parkinson's Disease.

The discovery of levodopa, a dopamine precursor, is considered the most significant breakthrough in medical treatment for PD (Elsworth, 2020). Levodopa, the gold standard for the treatment of PD symptoms, is commonly given to augment dopamine levels in PD patients (Connolly & Lang, 2014). Of note, carbidopa and benserazide are often given in combination to reduce the breakdown of L-DOPA in the peripheral system and increase central exposure and efficacy. The downside is that levodopa tends to induce dyskinesia and fluctuations in the majority of patients after a decade of being prescribed the medication. It also loses its efficacy

over time. In addition to levodopa, dopamine agonists (DA) are readily available and commonly prescribed. DAs mimic the effects of dopamine by interacting with dopamine receptors (Tan et al., 2022). The dopamine D2 receptor is the primary target of DAs, but different DAs can also affect serotonin and adrenergic receptors (Rizek et al., 2016). Examples of DAs include bromocriptine, apomorphine, rotigotine, pramipexole and ropinirole. DAs are ideal in early-onset PD due to the unwanted side effects levodopa may cause, such as dyskinesia. However, the advantages of using DA over levodopa in these cases wane over time (Zhang et al., 2023). Conversely, due to their tendency to cause psychiatric side effects, DAs are considered problematic in late-onset PD (Connolly & Lang, 2014).

In the CRISP study *Chapter 2* and *5*, whether being prescribed DAs is associated with psychiatric symptoms is investigated and discussed. Other classes of PD medications are available, like monoamine oxidase B (MAO-B) inhibitors, catechol-O-methyl transferase (COMT) inhibitors, and anticholinergics, in addition to miscellaneous medications such as amantadine (Tan et al., 2022). The first two classes aim to decrease dopamine metabolism and boost dopamine levels in the brain. Anticholinergics, on the other hand, are primarily utilized to control the unbalanced activity of acetylcholine and to assist in easing tremors and dystonia (Carlos Giugni & Rodriguez-Cruz, 2016). Eventually, PD patients will undoubtedly need several prescription alterations over time with the addition of adjunctive treatments. As no medication is available to modify the disease (Rizek et al., 2016), symptomatic treatment by the agents, as mentioned earlier, is the only option. Eventually, the effectiveness of these medications diminishes as the disease progresses. In advanced PD, the strategy remains the same: delivering continuous dopaminergic stimulation to tackle symptom fluctuations. As a result, more invasive options are introduced, including deep brain stimulation (Merola et al., 2011) and levodopa-carbidopa intestinal gel (Okun & Weintraub, 2013), to offer symptomatic treatment to these patients. DBS implantation, the focus of this thesis, is usually offered to a group of PD patients with specific characteristics. Patients are evaluated by a multidisciplinary team, including a neurologist, a neurosurgeon, a neuropsychiatrist, a neuropsychologist and PD nurses (Houeto et al., 2000). Based on current knowledge of the therapy and its efficacy, PD candidates may be divided into good, borderline, and poor (Rizek et al., 2016); see *Table 2*.

Table 2 Eligibility of PD Patients for DBS

Good candidates
• *An appropriate response to dopaminergic treatment*
• *On and off fluctuation is present.*
• *Those under 70 years of age.*
• *The quality of life is being affected by dyskinesia.*
• *A tremor that is not responsive to medication is present.*
• *There is evidence of reasonable cognitive function.*
Borderline candidates
• *A poor on-off dopaminergic response and the presence of severe dyskinesia*
• *On-off fluctuations accompany moderate cognitive function.*
• *Patients have on–off fluctuations with a poor response to dopamine replacement therapy.*
• *Moderate cognitive dysfunction and medication-resistant tremor*
• *A tremor that is resistant to medication and a poor response of on-off fluctuations to dopamine replacement therapy*
Poor candidates
• *The presence of severe dementia is evident.*
• *There have been reports of severe autonomic dysfunction.*
• *The dopamine response has been reported to be poor.*
• *Atypical parkinsonism*[3] .
• *There is an unstable psychiatric disease.*
• *There is a lack of a dedicated carer.*

[3] This is about conditions with similar symptoms and characteristics of PD (Gao et al., 2015).

1.2 Deep Brain Stimulation

Deep Brain Stimulation (DBS) is an alternative, invasive surgical treatment that uses surgically fixed electrodes to stimulate a specific target in the brain. These electrodes deliver electrical stimulation at a specific voltage, wavelength, and frequency. After implantation, these electrodes are connected to a pulse generator implanted beneath the clavicle bone using subcutaneous wires. As shown in *Figure* 4, a clinician can modify and adjust the stimulation using a wireless device connected to the pulse generator (Okun, 2012). The proposed mechanism suggests that instead of irreversible lesions caused by ablation surgeries, DBS causes reversible and adjustable lesions, resulting in adaptive modulation of neural activity (Ashkan et al., 2017). DBS's therapeutic mechanism depends on both the disease and the targets, which are usually deep-seated structures like subthalamic nuclei or white matter tracts such as fornix. Two reliable targets in the brain have been utilized for DBS in Parkinson's disease: the STN and the GPi. Much of the degenerative change in PD is located in the nuclei in the basal ganglia. The proposed mechanisms involve excitatory or inhibitory effects, oscillation adjustment, or a combination of both (Ashkan et al., 2017). The mechanism of DBS therapy could be indicated by the time required for stimulation to relieve symptoms. To illustrate, the rapid correction of pathological activity in the motor subcircuit is believed to be the cause of sudden stimulation-induced relief of tremor, whereas plasticity-related changes or other synaptic modifications are believed to be the reason for long-lasting effects of DBS on motor symptoms of PD after the device was switched off for several days (201,202). DBS effects in PD are also believed to extend beyond the immediate stimulation area and involve cortical-subcortical connectivity, especially in the motor cortex (De Hemptinne et al., 2015).

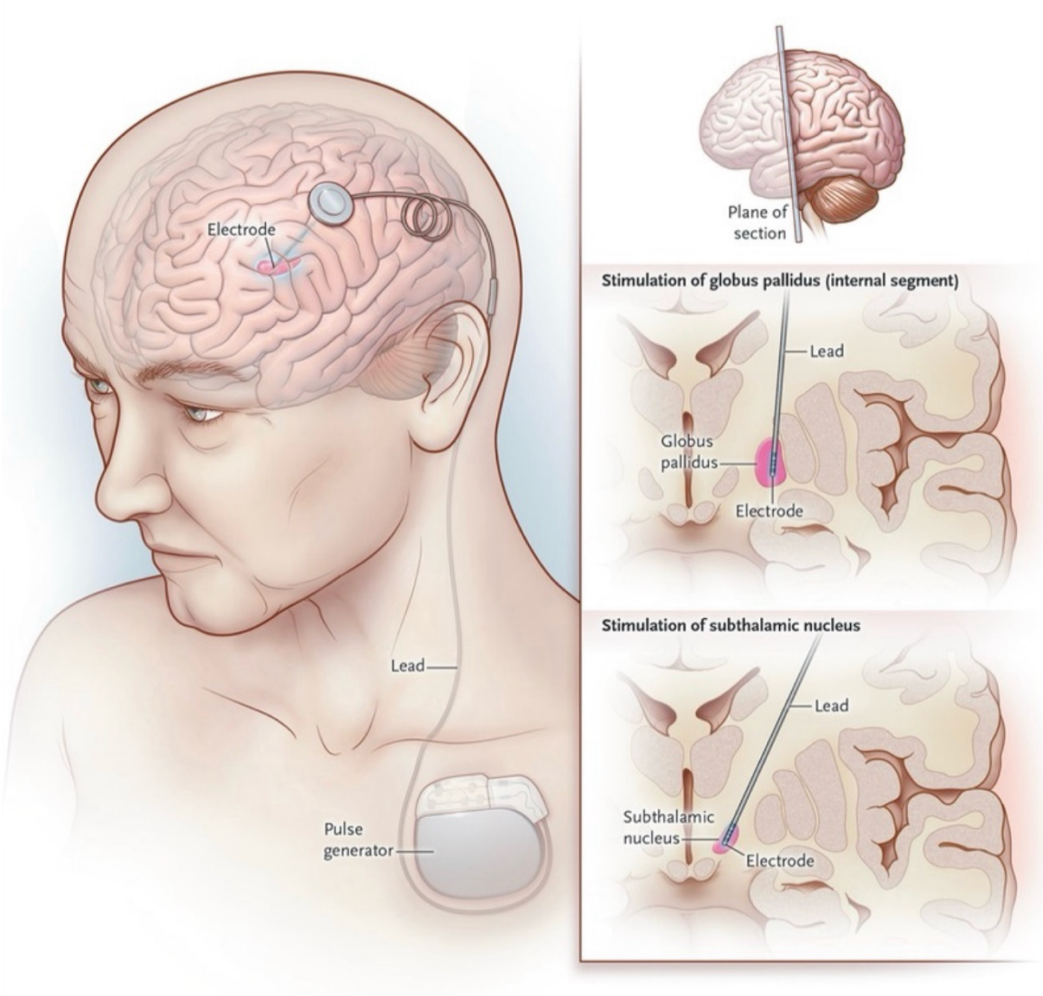


Figure 4 Demonstration of The Procedure of Electrode Implantation in Deep Brain Stimulation Therapy

1.2.1 Deep Brain Stimulation of Subthalamic Nucleus

The therapeutic approach of STN-DBS, which involves stimulating the subthalamic nucleus with deep brain stimulation, is a recognised treatment for PD and has been demonstrated to positively impact motor symptoms (Wagenbreth et al., 2019). In the CRISP Study, all patients with PD who undergo DBS for STN and GPi are recruited. However, due to the small number of DBS-GPi cases, their results are not included in this thesis. Further background information on DBS and STN is presented in *Chapter 2*, "Psychiatric Outcomes Following Deep Brain Stimulation in Parkinson's Disease: A Narrative Review".

1.3 Carer's Burden in Parkinson's Disease

The importance of considering carers' burden is immense since their role in maintaining quality care and management plans is substantial. Likewise, motor and non-motor symptoms can

impact the carer's general and mental well-being if not addressed. Carers can be spouses, offspring, siblings, close relatives, or professional carers. The term carer burden describes the multitude of physical, mental, and socioeconomic problems that arise when caring for somebody with a long-lasting and incapacitating illness (Zarit et al., 1980). Caring for someone with disabilities and limited independence may not only limit the carer's social and personal life, but the long-lasting stressful and demanding job may have an impact on their mental health (Modugno et al., 2020). The most important predictors of carer burden and stress in PD include disease severity, duration, cognitive dysfunction, and degree of disability (Aarsland et al., 2007). Psychiatric comorbidities in PD have also been strongly linked to caregiver distress (Aarsland & Karlsen, 1999). Two common behavioural disorders in PD, apathy and impulsivity, significantly increase the carer's burden (Leroi et al., 2012). Mood symptoms are also reported to impact carers (Juneja et al., 2020). Not only does the patient's condition affect carers, but also their coping skills, cultural and spiritual understanding, and the support they receive from health providers (Dekawaty et al., 2019; Greenwell et al., 2015; Pigott et al., 2022). The advanced treatment of PD, such as levodopa/carbidopa intestinal gel or continuous subcutaneous apomorphine infusion, has been shown to have a significantly more positive impact on a carer's mental health and burden (Modugno et al., 2020). In return, sufficient social and family support positively affects the quality of life and mood symptoms in PD patients (Ghorbani Saeedian et al., 2014). Therefore, due to their entangled relationship, it is necessary to include scales that assess carers' burden in studies like the CRISP study, which attempts to observe the effect of a treatment on symptoms of PD that directly affect the carer's burden.

Chapter 2: Psychiatric Outcomes Following Deep Brain Stimulation in Parkinson's Disease: A Narrative Review

2.1 Introduction

2.1.1 Association of Parkinson's Disease with Psychiatric Syndromes

Parkinson's disease (PD) is a neurodegenerative disorder that affects about 1% of people aged over sixty. Although PD is considered a movement disorder, psychiatric symptoms such as depression (Birchall et al., 2017), apathy (Robert et al., 2014), anxiety (Chang et al., 2012), disinhibition (Baig et al., 2019) and psychosis (Bordini et al., 2007) constitute core clinical features from the early stages; in some cases, they may precede the onset of motor symptoms (Combs et al., 2015). Compared to the non-PD population, psychiatric symptoms in PD tend to be more challenging to manage due to the need for integrated working between neuropsychiatry and neurology to achieve the best outcomes (Witt et al., 2008). This results from the complex interplay between their neurological and neuropsychiatric symptoms. In some clinical scenarios, the optimal management approach is a balancing act between adjusting both antiparkinsonian and psychotropic medication (Ferreri et al., 2006). Other services, such as neuropsychology and the allied healthcare professions (occupational therapy, physiotherapy, etc.), are equally crucial to ensuring the patients' full range of healthcare symptoms are met throughout their illness.

Psychiatric symptoms may predate or co-exist, with PD as a distinct separate condition. In such instances, the presence of PD may exacerbate psychiatric illness severity. They can also be a consequence of PD's underlying pathology, where their high prevalence compared to the population baseline suggests the latter to be the more significant of these two possibilities (Han et al., 2018). Further evidence comes from advanced imaging and post-mortem studies of PD patients; these have demonstrated a loss of serotonergic, noradrenergic, and dopaminergic function in the brains of those with PD (Hartmann, 2004), in line with the putative role of monoamine neurotransmitters signalling in anxiety and depression (Gallagher & Schrag, 2012). Psychosocial factors may also be relevant in mood changes related to medication. For instance, a medication that optimises motor function may improve mood via

increased physical ability, which is sufficient for the person with Parkinson's to leave the house and increase social interaction. The converse of such circumstance - increasing social isolation secondary to illness, being a strong predictor of depressive disorder (Ardle et al., 2022). The adverse effects of antiparkinsonian medications can also induce psychiatric symptoms such as impulsivity (Okai et al., 2013) and are of sufficient concern to fuel the ongoing search for alternative, more precisely targeted treatment strategies for PD (Jahanshahi et al., 2015).

2.1.2 Deep brain stimulation, A Hope for Fewer Therapeutic Side Effects?

Deep brain stimulation (DBS) is an established treatment for motor symptoms in PD (Frank et al., 2007). The procedure of DBS therapy has been explained in *chapter 1*. The subthalamic nucleus (STN) and internal globus pallidus (GPi) are the most common targets for DBS in PD, and both structures, aside from their role in motor control, play a significant role in cognitive and psychological functions, including reward processing (Mosley, Smith, et al., 2018). Located medially to the internal capsule, anteriorly to the thalamus, and dorsally to the substantial nigra, the STN has a regulatory role in movement. It receives inputs from the external Globus Pallidum (GPe) and projects excitatory glutaminergic neurons into the GPi to activate its inhibitory GABAergic neurons. These inhibitory GABAergic neurons project into the thalamus to reduce excitation of the thalamus and subsequently decrease movement (Mavridis et al., 2013). The STN also receives input from the medial prefrontal cortex, nucleus accumbens, the ventral tegmental area, and the limbic ventral pallidum (Gervais-Bernard et al., 2009). The medial tip of the STN projects to the limbic part of the substantia nigra and the ventral tegmental area. All these areas are known to have essential roles in inhibitory control, reward processing, learning and addictive behaviours. The STN and GPi prevent unwanted movements through this indirect pathway. There is further evidence to show they have an additional role in suppressing unwanted thoughts and behaviours, with pathology in these areas contributing to disinhibition (Rodriguez-Oroz et al., 2011). In other words, such structures play a role in both 'motion and emotion'.

PD patients are often presented with mild to moderate psychiatric symptoms such as depression, irritability, agitation, anxiety and apathy preoperatively (Porat et al., 2009; Smeding et al., 2006). By reducing the need for antiparkinsonian medication and improving quality of life, DBS may reduce PD-related psychiatric disorders, such as psychosis and depression, postoperatively. Conversely, in the postoperative period, DBS is also associated with *de novo* psychiatric symptoms (Vitek, et al., 2020) and depression, suicidal ideation,

apathy, and anxiety are reported to be more frequent among patients with poor post-DBS motor outcomes(Denheyer et al., 2009; Maier et al., 2016). However, their relationship with DBS stimulation parameters, patient characteristics, cognitive and behavioural outcomes are not yet established.

The exacerbation and development of new, (possibly) stimulation-dependent, psychiatric syndromes such as impulse control behaviours (ICBs) and hypomania after DBS therapy are variously reported (Porat et al., 2009; Smeding et al., 2006; Welter et al., 2014). Several papers have reviewed various aspects of a single or a group of related psychiatric symptoms. However, in most studies, the primary outcome has been a measure of motor rather than psychiatric function, with the inherent weakness in study design associated with secondary outcome data. Furthermore, relatively little is known of the factors most predictive of adverse psychiatric outcomes in DBS.

In this paper, we aim to provide a narrative review of the impact of DBS-PD on psychiatric symptoms in the PD population. We sought to answer three specific questions:

1. Does DBS worsen, improve, or have no impact on neuropsychiatric symptoms, including psychosis, depression, anxiety, apathy, and suicidality in this population,
2. To what extent do targeting and optimization of DBS parameters influence these psychiatric manifestations?
3. To what extent is the presence of neuropsychiatric symptoms predictive of DBS motor outcome and vice-versa? In doing so, we hoped to understand the relationship between psychiatric symptoms and post-DBS outcomes.

2.2 Methods

Based on the protocol registered on PROSPERO (CRD42020184000, See *Appendix 1 and 2*), we performed a comprehensive search on OVID/Embase, PsychInfo, Medline and PubMed separately on May 3rd and 4th, 2020, which was updated on August 3rd, 2022, and August 18th, 2023. The terms used in the original search are listed in *Table 3*.

Our inclusion criteria were studies that were original English papers only, studying the effects of deep brain stimulation (all brain targets) on adults with PD. Case reports were excluded,

while all experimental, prospective observational, retrospective, randomized and non-randomized clinical trials were included.

The Narrative review was reported according to the PRISMA review guidelines. AA, CW, and MB screened the abstracts and full-text entries. PS resolved any discrepancies. AA wrote the initial manuscript, which was reviewed by PS and DO.

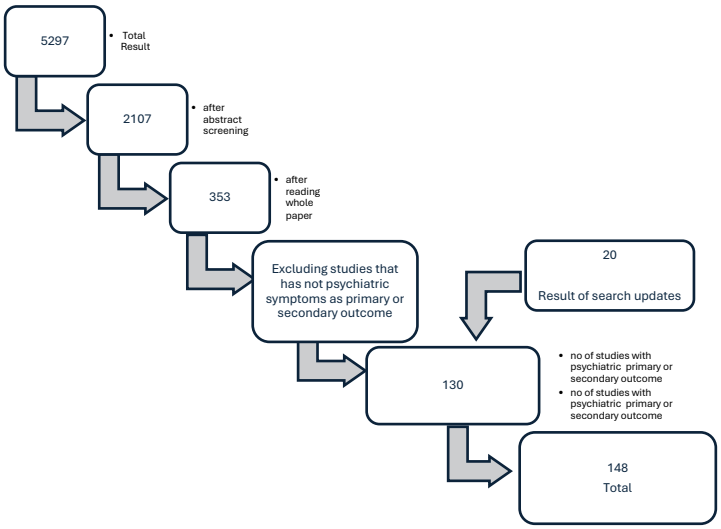


Figure 5 Process of Searching, Screening, and Splitting Result

Table 3 Search Terms and Columns

	Intervention/ DBS	**Population/ NDD**	**Focus/ Psychiatric disorders**
MESH Indexed	"Electrical brain stimulation", "deep brain stimulation"	"Neurodegenerative diseases", "Parkinson's Disease",	**"Obsessive-Compulsive Disorder", "Compulsive Behavior", "Compulsive behaviour", "Depressive Disorder, Major", "Depressive Disorder", "Depression", "Apathy", "Impulsive Behavior", "Behaviour, Impulsive" "Disruptive, Impulse Control, and Conduct Disorders", "Gambling", "Binge-eating disorder", "Hallucinations", "Delusions", "Suicide"[Mesh] OR "Suicide, attempted", "Suicide, Completed", "assessment, personality"**
KEYWORDS and Mapped terms	"Brain depth stimulation", "electrical brain stimulation", "deep brain stimulation", "electric stimulation therapy", DBS	"idiopathic Parkinson's disease" or "Lewy body Parkinson's disease" or "Parkinson's disease" or	**"Obsessive compulsive disorder", or "compulsive behavior", or ocd or "personality disorder", or depression or apathy or impulsivity or "impulsive behaviors" or "Impulsive control disorder" or ICD or "pathological gambling" or gambling or shopping or hypersexuality or "compulsive sexual behavior" or hobbyism or "binge eating disorder" or "eating behavior" or punding or "dopamine dysregulation syndrome" or psychosis or hallucination or delusion or suicide or "suicidal ideation" or anxiety or Personality traits**

**: Mapped terms on Ovid/Embase/PsycINFO/Medline where each database may offer different mapped terms for each subject.*

Search Databases: PubMed (MeSH + Keyword) + OVID/Embase/PsycINFO/Medline (Mapped terms + keywords)

2.3 Results

Our original search found a total number of 5,297 papers (*Figure 5*). After a double-phase screening, 353 papers ultimately met our inclusion criteria. In both phases, irrelevant papers were removed. A total of 148 studies relevant to post-DBS psychiatric results were identified. Five papers were additionally added as they were already known to the authors via consultation with individuals with expertise in the field. The narrative review was conducted based on themes from our findings (See *Appendix 3*), including 1- Relationships between pre-existing psychiatric symptoms and post-DBS motor and psychiatric outcomes, 2- Early postoperative effects of DBS, 3- Long-term effects of DBS on psychiatric symptoms, 4- Risk factors and predictors of DBS psychiatric outcomes, 5- Comparing psychiatric outcomes between DBS targets, 6- DBS psychiatric outcomes vs. alternative treatments and lastly 7- Optimization of DBS parameters for psychiatric outcomes. It is noteworthy to add that the ranking of studies in synthesis writing for results under each subsection was based on their focal strength on psychiatric symptoms, cohort size, and the presence of a control group. This was intended to prioritize studies that were of higher quality when presenting results.

2.3.1 Methodological Characteristics

Study designs included case-control studies (N=18), prospective cohort studies (N=74), retrospective (N=30), experimental studies (N=5), cross-sectional (N=6), randomised clinical trials (RCTs) (N=16) and non-randomised trials (N=4). Of the 148 studies included in this manuscript, 94% focused on bilateral STN-DBS. Therefore, we use DBS to refer to STN-DBS unless otherwise specified. As mentioned above, studies are narrated based on their quality in terms of design and cohort (See *Appendix 2*).

2.3.2 Early Postoperative Effects of DBS

In total, 39 papers have reported early postoperative psychiatric adverse events (AEs), indicating that immediate postoperative psychiatric adverse events, such as psychosis, depression, and anxiety, are common (Herzog et al., 2003). Most psychiatric AEs tended to occur in the first few days after the operation and were primarily transient. These AEs reportedly improved after parameter adjustment or adjustment or/and the introduction of

dopaminergic, antipsychotic and antidepressant medications (Herzog et al., 2003; Janssen et al., 2014; Kalteis et al., 2006; Thobois et al., 2002). In this section, the varied information provided on early postoperative psychiatric AEs is presented. Subsequently, identified risk factors for postoperative psychiatric AEs will be discussed.

SUMMARY POINTS: Early Postoperative Psychotic AEs

- Psychotic symptoms are not uncommon after DBS (5-25%).
- The onset may coincide with surgery or apomorphine withdrawal.
- The onset ranges from intraoperative period to weeks after.
- Antipsychotics are reportedly helpful.

2.3.2.1 Psychosis and Altered Consciousness

Sixteen studies reported various early postoperative episodes of psychosis and altered consciousness. It should be noted that most studies were prospective and cohorts ranging from 30-100 participants (Buhmann et al., 2017; Contarino et al., 2007; Gervais-Bernard et al., 2009; Herzog et al., 2003; Houeto et al., 2002; Kalteis et al., 2006; Krack et al., 2003; Liang et al., 2006; Paim Strapasson et al., 2019; Radziunas et al., 2020; Schupbach et al., 2005; Smeding et al., 2006; Thobois et al., 2010; Tir et al., 2007; Witt et al., 2011; Zibetti et al., 2007). The retrospective studies produced findings similar to those of the prospective studies but also provided specific details of AEs and their prognosis (Radziunas et al., 2020). Most studies reported symptoms consistent with altered or fluctuating levels of consciousness consistent with delirium, with alterations in thought, sensory modalities, and behaviour (Liang et al., 2006; Paim Strapasson et al., 2019; Schupbach et al., 2005; Zibetti et al., 2007). For example, acute onset, non-systematised, and fluctuant psychotic symptoms were documented in the context of postoperative transient confusion at rates of 2-26% by two prospective (N=71) and one retrospective study (N=49)(Kalteis et al., 2006; Paim Strapasson et al., 2019; Zibetti et al., 2007). Transient psychosis in the context of delirium was

separately recorded at a rate of 10% in two prospective cohort studies (N=33, N=37)(Liang et al., 2006; Schupbach et al., 2005).

The prevalence of psychotic disorders and altered consciousness ranged between 5% and 26%, including; transient confusion 10-26% (Buhmann et al., 2017; Paim Strapasson et al., 2019; Zibetti et al., 2007), transient delirium 9-24% (Krack et al., 2003; Liang et al., 2006; Tir et al., 2007), transient hallucination 7-16%(Gervais-Bernard et al., 2009; Schupbach et al., 2005), non-bizarre delusion 11% (Radziunas et al., 2020), unspecified transient psychotic episode 1.5-10% (Contarino et al., 2007; Herzog et al., 2003; Kalteis et al., 2006; Radziunas et al., 2020; Schupbach et al., 2005; Thobois et al., 2010; Witt et al., 2008) and transient aggressive behaviours 8% (Buhmann et al., 2017; Contarino et al., 2007; Herzog et al., 2003; Radziunas et al., 2020; Schupbach et al., 2005; Zibetti et al., 2007).

Furthermore, less common neuropsychiatric events such as lethal catatonia have also been reported by a prospective cohort study (N=91) at 1% (Tir et al., 2007). Regarding the time of onset, most psychotic episodes occurred in the first few days following the operation (Buhmann et al., 2017). Some psychotic episodes were reported following electrode implantation (Buhmann et al., 2017; Kalteis et al., 2006; Krack et al., 2003; Liang et al., 2006; Tir et al., 2007), whereas others were linked to factors other than the DBS operation (Houeto et al., 2002; Qureshi et al., 2015). For example, one patient developed florid psychosis postoperatively following withdrawal of their subcutaneous apomorphine (Houeto et al., 2002).

It is noteworthy that psychotic events are also reported several weeks after the operation, prior to switching the stimulation on. In a consecutive case series of patients with GPi-DBS (N=18; unilateral and bilateral), one patient was reported to have developed a psychotic episode three weeks after the operation (Lachenmayer et al., 2019). The authors did not explain the potential cause behind the psychotic event in their cohort. Finally, when compared to medical treatments, psychotic events were reported to be less common after DBS operation, presumably due to the reduction observed in dopamine replacement therapy (DRT), as psychotic episodes were reported in 5% of the STN-DBS group (n=78) versus 9% in the Best Medical Treatment (BMT) group (n=78) in a randomized clinical trial (Witt et al., 2008).

Regarding the prognosis of early postoperative AEs, four studies indicated that early postoperative AEs were reversible (Gervais-Bernard et al., 2009; Radziunas et al., 2020;

Smeding et al., 2006; Tir et al., 2007). In a case-control study (n=99, control n=35), psychotic AEs reported (likely delirium-related) among 9% of study participants were managed by using antipsychotics (Radziunas et al., 2020). Transient psychosis in the context of delirium among participants of a case-control study (case=22, control=18) also resolved in the first two months after antipsychotic intervention (Gervais-Bernard et al., 2009; Radziunas et al., 2020; Smeding et al., 2006; Tir et al., 2007). One intriguing consecutive case series involved a treatment centre that used clozapine to treat transient hallucinations and confusion (N=42) in the first three months postoperatively (Gervais-Bernard et al., 2009). Treatment was not always necessary for postoperative psychotic AEs as a prospective study (N=100) reported that postoperative transient delirium[4] (16%) primarily resolved in a few days without any intervention (Tir et al., 2007).

SUMMARY POINTS: Early Postoperative Mood and Apathy AEs

- Mood alterations and apathy symptoms are common after DBS (10-45%).
- Such mood AEs range from feeling sad to a hypomanic episode, and are mostly transient.
- Apathy symptoms tend to be more persistent.

QUICK TIPS

2.3.2.2 Mood Disorders and Apathy

Eleven studies reported early postoperative mood changes (Buhmann et al., 2017; Gervais-Bernard et al., 2009; Houeto et al., 2002; Krack et al., 2003; Li et al., 2015; Liang et al., 2006; Radziunas et al., 2020; Schupbach et al., 2005; Welter et al., 2014; Witt et al., 2008). About one-third of participants in a prospective study (N=33) reported that they experienced mood changes in the days following the operation (Liang et al., 2006). Retrospective studies have reported a higher prevalence of mood disturbances. A retrospective study (N=109) reported that depression symptoms developed a few days after the operation in 42% for STN (n=42) and at a similar frequency in both the GPI (n=10, 60%) and ventralis intermediate

[4] Transient delirium was reported to range from clouding consciousness to psychosis (Tir et al., 2007).

nucleus (n=12, 58%) (Pinsker et al., 2013). Another retrospective study reported that among GPi-DBS (N=20), the rate for each of depression and anxiety was 10% each (Buhmann, Huckhagel, Engel, Gulberti, Hidding, Poetter-Nerger, Goerendt, Ludewig, Braass, Choe, et al., 2017).

Of note, the authors used recorded psychiatric AEs as an indicator of the presence of postoperative mood change. In retrospective studies, the source of data and collection method can affect the result. The small size of the GPi cohort in both studies is also noteworthy. A lower rate (10%) of emotional lability was also observed by another prospective study (N=37) postoperatively (Schupbach et al., 2005). As a result, in extreme cases, these mood changes prevented patients from being discharged. Severe anxiety with fear (n=1) and non-bizarre delusion (n=2) were reported in a prospective study (N=22) to prolong hospital stay. (Radziunas et al., 2020; Schupbach et al., 2005)

Not only the prevalence but the course of postoperative depression reportedly varies between studies. Prospective studies have found that depression is more likely to persist (2.6-20%) than be transient (5-13%). A prospective study (N=37) found that depression was transient in 8% and permanent in 20% of participants (Schupbach et al., 2005). However, depression is found to be primarily transient in larger studies. A randomised clinical trial reported that in the STN-DBS group (n=78), 5% of participants developed depression compared to none in the Best Medical Treatment (BMT) group (n=78), which remitted in the six-month follow-up postoperative period (Witt et al., 2008). Others in two prospective cohort studies (N=273) consistently reported only transient depression among 2-13% of participants(Buhmann et al., 2017; Li et al., 2015).

Other mood disorders were also reported. *De novo* hypomania was reported following the DBS operation at a rate of 4-10% (Contarino et al., 2007; Gervais-Bernard et al., 2009; Houeto et al., 2002; Janssen et al., 2014; Krack et al., 2003; Li et al., 2015; Schupbach et al., 2005; Smeding et al., 2006). The postoperative transient hypomania rate was reported at 10% in a consecutive case series (N=176) (Welter et al., 2014) and a prospective cohort study (N=195) (Li et al., 2015). In one prospective cohort study (N=37), transient hypomania (8% of cases) subsided in half the patient population after stimulation activation (Schupbach et al., 2005). A separate study found that the hypomania, which was observed in two out of forty-two patients (5%) in the first month following the procedure, did not subside after the stimulation was activated (Gervais-Bernard et al., 2009), indicating a possible weak connection between the symptom and the stimulation.

Transient and moderate euphoria was also reported by another smaller prospective study a few days after the operation among 75% of patients (N=24), but only one patient (4%) developed hypomania, which resolved spontaneously after two weeks (Houeto et al., 2002). Postoperative mania was also reported in relatively small cohorts (N=16 and 22) at 1-7% (Contarino et al., 2007; Smeding et al., 2006). A 6-month case-control study (n=99, control n=35) reported a *de novo* mania rate, requiring clinical intervention, at 1% (Smeding et al., 2006).

Finally, early postoperative apathy was also reported by four studies (Contarino et al., 2007; Janssen et al., 2014; Krack et al., 2003; Schupbach et al., 2005). Immediate postoperative persistent apathy was reported in 4-10% of participants in three prospective cohort studies (Janssen et al., 2014) (N=87) (Contarino et al., 2007; Schupbach et al., 2005). Moreover, in a consecutive case series, early *de novo* apathy had become permanent in 10% of participants (N=49) when measured five years after the operation (Krack et al., 2003).

2.3.2.3 Suicidal Ideation and Suicide

Suicidal ideation and suicide attempts within days of operation were reported in five studies (N=300), with a prevalence ranging from 1% to 13% (Berney et al., 2002; Buhmann et al., 2017; Porat et al., 2009; Schupbach et al., 2005; Witt et al., 2008). A randomised clinical trial reported a single case of completed suicide (1%) in their STN-DBS group (n=78), in comparison to none in the BMT group six months after the operation (n=78)(Witt et al., 2008). Furthermore, another prospective study reported no suicide in their STN group (n=78), but they reported one completed suicide (5%) among the smaller GPi-DBS group (n=20)(Buhmann, Huckhagel, Engel, Gulberti, Hidding, Poetter-Nerger, Goerendt, Ludewig, Braass, Choe, et al., 2017). A prospective study (n=37) and a consecutive case series (n=24) reported that 10-12% of the STN-DBS cohort had a suicide attempt in the weeks following the operation(Berney et al., 2002; Schupbach et al., 2005). The smaller cohort size of the two studies may account for the greater rate. As for the time of onset, a similar study (n=22) reported that a patient (4%) completed suicide three months after the operation despite motor improvement (Porat et al., 2009), suggesting that there is a risk of suicide even weeks after the operation.

SUMMARY POINTS: Risk Factors for Early Psychiatric AEs

- Age, cognitive function and history are patient related risk factors.
- Older age is associated with confusion postoperatively.
- Fewer number of electrodes passes may reduce the risk.

2.3.2.4 Risk Factors for Immediate Psychiatric Adverse Effects Following DBS Surgery

Age, impaired cognition, and preoperative history of psychiatric symptoms were found to be potential risk factors for developing postoperative psychiatric AEs (Abulseoud et al., 2016; Berney et al., 2002; Lhommée et al., 2012; Paim Strapasson et al., 2019; Pilitsis et al., 2005; Porat et al., 2009). Studies with smaller cohorts have tried to identify more potential predictive factors intraoperatively, such as theta oscillation in the STN region for postoperative hypomania (Chen et al., 2021).

Of note, a secondary analysis of the results of an RCT study found that the number of electrode passes[5] was associated with irritability up to six months postoperatively, a common finding following DBS patients (Burdick et al., 2011). These scores remained unchanged during blinded on/off status in both GPi and STN, indicating the lasting effect of lesions on irritability. Such findings were not replicated in other smaller cohorts of the STN (n=33) and GPi DBS (n=15) (Thobois et al., 2010).

A retrospective study (N=49) reported that younger age increased the risk of psychiatric complications, but this did not reach statistical significance (Paim Strapasson et al., 2019). More specifically, a prospective study (N=59) found that older age was associated with a higher risk of confusion after the operation (Abulseoud et al., 2016).

[5] Passes are referred to number of insertions of the microelectrode to reach the target on each side of the brain. It usually requires 1-5 passes to reach the optimal location, such as STN (Vinke et al., 2022).

Moreover, in addition to preoperative depression, which was reported by a prospective cohort study (Abulseoud et al., 2016), one retrospective study found that postoperative confusion was also correlated to preoperative frontal-subcortical impairment, including cognition, mood, and motor skills (Pilitsis et al., 2005). Postoperative confusion was also significantly associated with a score on the Charlson Comorbidity Index[6], according to a retrospective cohort study (N=49) (Paim Strapasson et al., 2019).

A consecutive case series study (N=63) reported that, unlike apathy at 12 months, earlier postoperative apathy and depression were lower when patients were on medication and the DBS was switched on (Lhommée et al., 2012). As for suicidality, a consecutive case series (N=24) reported that two-thirds of patients with postoperative depression and suicidality had a history of depression, but none had a history of suicidality (Berney et al., 2002). On the contrary, in a prospective cohort (N=22), a patient (4%) who completed suicide three months later had a history of preoperative suicidal ideation (Porat et al., 2009).

2.3.3 Long-Term Effects of DBS on Psychiatric Symptoms

The long-term effects of DBS on psychiatric symptoms varied significantly between studies as well as within the same populations. Some studies reported individual cases separately from their main cohorts; these are not included in our review. The onset, course, and potential risk factors are reviewed for each symptom category. The instruments used to measure symptoms have also been mentioned (when provided by the authors).

[6] Charlson Comorbidity Index was developed to predict mortality in patients with comorbidities.

SUMMARY POINTS: Long-term Effects on Psychotic Symptoms

- Psychotic symptoms tend to return to baseline.
- Psychotic symptoms are less common after DBS than medical treatments

2.3.3.1 Psychosis and Altered Consciousness

Six studies reported on preoperative psychosis (Castelli et al., 2006; Funkiewiez et al., 2004; Kaiser et al., 2008; Lilleeng et al., 2015; Tao & Liang, 2015; Yoshida et al., 2009). Two studies (N=149) reported worsening (Castelli et al., 2006; Funkiewiez et al., 2004), one study (N=33) reported no change (Kaiser et al., 2008) and three studies, including two retrospective and one consecutive case series (N=76), reported mainly improvement (Lilleeng et al., 2015; Tao & Liang, 2015; Yoshida et al., 2009). Two consecutive case series (N=72 and N=77) using the Unified Parkinson's Disease Rating Scale (UPDRS), part one, showed deterioration on the 'thought disorder' item fifteen months postoperatively. However, only one patient met the criteria for psychosis (Castelli et al., 2006; Funkiewiez et al., 2004). The deterioration in psychotic disorders stabilized before returning to baseline value after three years, as reported by another prospective cohort study (N=33) (Kaiser et al., 2008). However, undergoing STN-DBS was associated with a decrease in the incidence of hallucinations in comparison with medically treated patients one year after the operation, again, presumably due to a reduction of DRT (Kaiser et al., 2008; Lilleeng et al., 2015).

2.3.3.2 Mood Symptoms

A summary of our results is shown in *Table 4 and Figure 6*. Among our results, twenty-five studies have reported DBS effects on mood beyond 12 months following the operation (Acera et al., 2019; Castelli et al., 2008; Chang et al., 2012; De Chazeron et al., 2016; Fasano et al., 2010; Funkiewiez et al., 2004; Gruber et al., 2019; Harati & Muller, 2013; Heo et al., 2008; Houeto et al., 2002; Janssen et al., 2014; Jost et al., 2021; Kaiser et al., 2008; Kalteis et al., 2006; Kishore et al., 2010; Lewis et al., 2015; Lezcano et al., 2016; Lhommée et al., 2012; Lilleeng et al., 2015; Morrison et al., 2004; Porat et al., 2009; Rizzone et al., 2014; Wang et al., 2009; Welter et al., 2014; Zibetti et al., 2007). Mood symptoms were globally improved

among 534 participants 1-11 years after the operation (Chang et al., 2012; Kaiser et al., 2008; Kalteis et al., 2006; Rizzone et al., 2014; Wang et al., 2009). In a subset of studies, the initial improvement returned to baseline level 1-3 years after the operation (Chang et al., 2012; Kaiser et al., 2008; Kalteis et al., 2006; Wang et al., 2009). In addition, fewer off-period dysphoric mood changes, on-period euphoric behaviours, depression, hypomania, and anxiety disorders such as panic attacks, agoraphobia and social phobia were reported 1-11 years after DBS operation by some studies.(Castelli et al., 2008; Chang et al., 2023; Funkiewiez et al., 2004; Houeto et al., 2006; Kalteis et al., 2006; Lezcano et al., 2016; Lhommée et al., 2012; Lilleeng et al., 2015; Rizzone et al., 2014; Wang et al., 2009)

However, other studies did not observe such improvements. No significant changes in psychiatric symptoms were reported, including depression (Acera et al., 2019; Fasano et al., 2010; Harati & Muller, 2013; Heo et al., 2008; Janssen et al., 2014; Jiang et al., 2022; Jost et al., 2021; Kishore et al., 2010; Lewis et al., 2015; Morrison et al., 2004; Porat et al., 2009; Rizzone et al., 2014; Welter et al., 2014), anxiety (Fasano et al., 2010; Gruber et al., 2019; Jiang et al., 2022; Jost et al., 2021; Kishore et al., 2010), emotional well-being (Kishore et al., 2010; Zibetti et al., 2007) and manic symptoms (De Chazeron et al., 2016) up to eight years after the operation. These results across several studies with a wide range of cohort sizes (6-121 participants, *table* 4) and diverse study designs suggest that mood symptoms tend to remain unchanged over the long term. The neuropsychiatric inventory (Porat et al., 2009) and Hamilton anxiety rating scale (Okun et al., 2014) mainly showed early worsening of anxiety, whereas the Zung anxiety scale (ZAS) (Fasano et al., 2010) and Beck's anxiety inventory (BAI) (Lhommée et al., 2012) have shown improvement. In the same study, clinician-rated depression on the Montgomery and Asberg depression rating scale and patient-rated Multidimensional Mood State Questionnaire (MDMQ) showed improvement, whereas depression on patient-rated Beck's Depression Inventory (BDI) showed deterioration (Gruber et al., 2019). When recruiting from different DBS centres and using different rating scales, discrepancies were seen in studies. A long-term prospective study (N=26) reported significant improvement in anxiety after 11 years among the population from one centre but not the other participating centre (Rizzone et al., 2014). The authors did not explain this, although it could have been related to differences in PD severity or demographic differences. Of note, there were not many differences in scores between the raters (Gruber et al., 2019). Self-reported BDI scores positively correlated with clinician-rated MADRS scores at an average of 6 years postoperatively (N=36) (Gruber et al., 2019). Higher-quality studies that use the most sensitive

and specific scales with frequent long-term follow-ups are necessary to better understand the effect of DBS on individual mood symptoms.

A discrepancy between early and late follow-ups may indicate less benefit during the first three months after the STN-DBS operation. The DBS effect beyond 12 postoperative months yielded different results; hence, they are summarised in two subsections below. No improvement in mood and behaviours was observed beyond five years.

SUMMARY POINTS: Long-term Effects on Mood Symptoms < 12 Months

- Depression symptoms mainly range from stable to improvement.
- On/off stimulation status has little immediate effect on Mood.
- Anxiety tends to reduce postoperatively.
- Improvement in mood can be related to the improved QoL

2.3.3.2.1 Within 12 Months Following the Operation

Two RCTs, one experimental case-control study, and four prospective studies reported no change in depression and anxiety among a total of 425 participants 3 to 12 months after the operation (Boel, Odekerken, Geurtsen, et al., 2016; Castelli et al., 2006; Heo et al., 2008; Krause et al., 2022; Lewis et al., 2015; Morrison et al., 2004; Vitek, et al., 2020). Whereas two case-control, four consecutive case series and three prospective cohort studies reported worsening of depression, anxiety, and mania among a total of 243 subjects 3-12 months after the operation (Berney et al., 2002; Bordini et al., 2007; Kim et al., 2013; Lewis et al., 2015; Porat et al., 2009). Finally, three prospective studies reported improvement in mood symptoms 6 months after the operation among 209 patients postoperatively (Antosik-Wójcińska et al., 2017; Birchall et al., 2017; Chang et al., 2023; Chopra et al., 2014; Houeto et al., 2002; Straits-Troster et al., 2000). Despite the majority reporting improvement, it is essential to note that the cohorts are small, and the study designs and assessment tools are heterogeneous. In a double-blinded, randomized clinical trial (RCT), participants were randomised into either therapeutic STN-DBS (n=121) or subtherapeutic STN-DBS (n=39) group for three months. The authors reported that depression scores did not change after 3 months in either group (Vitek, et al., 2020). Another RCT (GPi n=65, STN n=63) reported no

change in anxiety and depression within one year following STN and GPi stimulation (Boel, Odekerken, Geurtsen, et al., 2016). In prospective and retrospective studies (N=77), no change was reported when comparing depression scores between stimulation on and off periods (Castelli et al., 2006; Morrison et al., 2004). As stated earlier, there is a commonality among other cohorts that their size is not greater than 50 participants in all studies (Heo et al., 2008; Lewis et al., 2015).

On the other hand, there are reports that DBS can negatively impact mood symptoms on both self-rating and clinician-rating scales. A randomized clinical trial (unilateral STN n=16 vs. unilateral GPi n=14) revealed significant worsening of anxiety, depression and mania postoperatively in both groups at 2-month follow-up (Okun et al., 2014). A prospective study reported that the cognitive component of the depression scale worsened. When a cohort of seventeen patients of STN-DBS was compared to 22 matched PD patients before and 6 months after the stimulation, while psychical symptoms of depression remained stable for both groups, a significant difference was reported in cognitive-emotional symptoms of depression on the BDI (item 1-9 and 13-15) in favour of the latter group (Strutt et al., 2012). In longer follow-ups, *de novo* depression was experienced by nearly half of the participants in a prospective study (N=12) twelve months postoperatively (Houeto et al., 2002). For anxiety in particular, state anxiety[7] showed improvement at one month postoperatively in a case-control study, but trait anxiety[8] significantly worsened 3-12 months after operation (N=31) (Chang et al., 2012). Preoperative agoraphobia also worsened after the operation in two out of four patients in a small prospective cohort study (N=24) (Houeto et al., 2002). These studies had a smaller cohort than those that reported no change in mood scores.

Others have found positive results. A consecutive case series (N=50) reported significant improvement in depression scores six months after unilateral STN-DBS, suggesting that unilateral stimulation is better for mood symptoms (Birchall et al., 2017). During the first 6-12 months after the operation, two prospective cohort studies (N=111) (Antosik-Wójcińska et al., 2017; Chopra et al., 2014)and a retrospective study (N=108) (Chang et al., 2023) found improvements in anxiety and depression. For anxiety symptoms, a non-consecutive case series (N=14) reported significant improvement in anxiety physiological subscores on the HAM-A (Somma et al., 2022). The authors suggest that this could be because of over-optimism

[7] Current anxiety

[8] Predisposed tendency to present with state anxiety.

regarding DBS effects or biased attribution of anxiety improvement to overall PD improvement since it was reported by clinicians, not patients (Somma et al., 2022).

SUMMARY POINTS: Long-term Effects on Mood Symptoms > 12 Months

- Mood symptoms tend to improve compared to baseline.
- Off/On-period dysphoric/euphoric mood and anxiety reduced.
- Beyond 5 years after surgery, mood remains mostly stable.
- Improvement in mood is relatable to the improved QoL.

2.3.3.2.2 Beyond 12 Months Following the Operation

Among our results, twenty-five studies have reported DBS effects on mood beyond 12 months following the operation (Acera et al., 2019; Castelli et al., 2008; Chang et al., 2012; De Chazeron et al., 2016; Fasano et al., 2010; Funkiewiez et al., 2004; Gruber et al., 2019; Harati & Muller, 2013; Heo et al., 2008; Houeto et al., 2002; Janssen et al., 2014; Jost et al., 2021; Kaiser et al., 2008; Kalteis et al., 2006; Kishore et al., 2010; Lewis et al., 2015; Lezcano et al., 2016; Lhommée et al., 2012; Lilleeng et al., 2015; Morrison et al., 2004; Porat et al., 2009; Rizzone et al., 2014; Wang et al., 2009; Welter et al., 2014; Zibetti et al., 2007). Mood symptoms were globally improved among 534 participants 1-11 years after the operation (Chang et al., 2012; Kaiser et al., 2008; Kalteis et al., 2006; Rizzone et al., 2014; Wang et al., 2009). In a subset of studies, the initial improvement returned to baseline level 1-3 years after the operation (Chang et al., 2012; Kaiser et al., 2008; Kalteis et al., 2006; Wang et al., 2009). In addition, fewer off-period dysphoric mood changes, on-period euphoric behaviours, depression, hypomania, and anxiety disorders such as panic attacks, agoraphobia and social phobia were reported 1-11 years after DBS operation by some studies.(Castelli et al., 2008; Chang et al., 2023; Funkiewiez et al., 2004; Houeto et al., 2006; Kalteis et al., 2006; Lezcano et al., 2016; Lhommée et al., 2012; Lilleeng et al., 2015; Rizzone et al., 2014; Wang et al., 2009)

However, other studies did not observe such improvements. No significant changes in psychiatric symptoms were reported, including depression (Acera et al., 2019; Fasano et al.,

2010; Harati & Muller, 2013; Heo et al., 2008; Janssen et al., 2014; Jiang et al., 2022; Jost et al., 2021; Kishore et al., 2010; Lewis et al., 2015; Morrison et al., 2004; Porat et al., 2009; Rizzone et al., 2014; Welter et al., 2014), anxiety (Fasano et al., 2010; Gruber et al., 2019; Jiang et al., 2022; Jost et al., 2021; Kishore et al., 2010), emotional well-being (Kishore et al., 2010; Zibetti et al., 2007) and manic symptoms (De Chazeron et al., 2016) up to eight years after the operation. These results across several studies with a wide range of cohort sizes (6-121 participants, *table 4*) and diverse study designs suggest that mood symptoms tend to remain unchanged over the long term. The neuropsychiatric inventory (Porat et al., 2009) and Hamilton anxiety rating scale (Okun et al., 2014) mainly showed early worsening of anxiety, whereas the Zung anxiety scale (ZAS) (Fasano et al., 2010) and Beck's anxiety inventory (BAI) (Lhommée et al., 2012) have shown improvement. In the same study, clinician-rated depression on the Montgomery and Asberg depression rating scale and patient-rated Multidimensional Mood State Questionnaire (MDMQ) showed improvement, whereas depression on patient-rated Beck's Depression Inventory (BDI) showed deterioration (Gruber et al., 2019). When recruiting from different DBS centres and using different rating scales, discrepancies were seen in studies. A long-term prospective study (N=26) reported significant improvement in anxiety after 11 years among the population from one centre but not the other participating centre (Rizzone et al., 2014). The authors did not explain this, although it could have been related to differences in PD severity or demographic differences. Of note, there were not many differences in scores between the raters (Gruber et al., 2019). Self-reported BDI scores positively correlated with clinician-rated MADRS scores at an average of 6 years postoperatively (N=36) (Gruber et al., 2019). Higher-quality studies that use the most sensitive and specific scales with frequent long-term follow-ups are necessary to better understand the effect of DBS on individual mood symptoms.

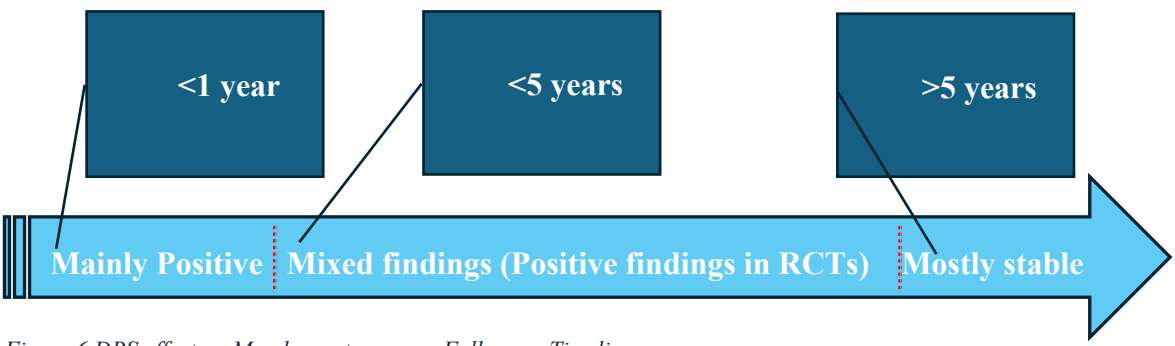


Figure 6 DBS effect on Mood symptoms on a Follow-up Timeline

Table 4 Studies of DBS Effect on Mood Symptoms Stratified by Outcome, Follow-Up Period, and Study Design (Multi Colour Highlights)

	Prospective Cohort **Randomized Clinical Trial** **Retrospective** **Consecutive Case Series** **Case-control Study**					
	Follow-up Periods					
	3 months	**6 months**	**1 year**	**1-3 years**	**3-6 Years**	**≥6 year**
No change/ insignificant change	**1-BDI** Therapeutic n=121 and subtherapeutic *DBS* n=139(Vitek, et al., 2020) 2-**BDI** N=22(Porat et al., 2009)* 3- BDI N=60 70% no change (Castelli et al., 2006) 4-**GDI** n=17 (control matched PD (n=11) (Morrison et al., 2004)		**1-HADS** *GPi* n=65, *STN* n=63(Boel, Odekerken, Geurtsen, et al., 2016) 2-**BDI** N=20 (Harati & Muller, 2013) 3-**BDI-II** N=27(Lewis et al., 2015) 4-**BDI** N=46(Heo et al., 2008) 5-**BDI+MADRS** N=34(De Chazeron et al., 2016) 6-**MADRS** N=262(Welter et al., 2014) 7-BDI II (N=43) (Krause et al., 2022)	**1-BDI** N=19 74% stable, 26% improv17 months postop(Castelli et al., 2008) 2-**POMS + STAI** N=33, the improved symptoms returned to baseline 36 months postop (Kaiser et al., 2008) 3--**HAMD** and **SDS** N=27 no change 6-18 months postop (Wang et al., 2009)* 4-**UPDRS-I** N=36(Zibetti et al., 2007) 5-**BDI** N=20(Harati & Muller, 2013) 6-HADS (STN-DBS n=75, BMT n=84)(Jost et al., 2021)	1-**MADRS** N=69(Lezcano et al., 2016)* 2-**BDI**, **HADS** N=45(Kishore et al., 2010) 3-**MADRS** N=50(Acera et al., 2019)	1-**BDI-II** N==14 *(Janssen et al., 2014) 2-**BAI+BPRS** N=79 (compared to preop)(Gruber et al., 2019)* 3-**ZDS+ZAS** N=20(Fasano et al., 2010) 4-**BDI+ZDS** N=26 (Rizzone et al., 2014) 5-HAM-A, HAM-D (N=27) *(Jiang et al., 2022)
Improved	**1-BDI** pallidal n=9 *thalamus* n=7(Straits-Troster et al., 2000) 2-**BRMES** N=33(Kalteis et al., 2006)*	**1-MADRS, HAM-D, BDI** *STN-DBS* N=60(Antosik-Wójcińska et al., 2017)	1-**BDI + BAI** *STN* N=63(Lhommée et al., 2012) 2- **BDI-II** N=26*(Janssen et al., 2014) 3-**BRMES + HAM-A** N=33(Kalteis et al., 2006)*	1-**BDI** n=77(Funkiewiez et al., 2004) 2-**MADRS < BAS –** N=20(Houeto et al., 2006)	1-**MINI** *STN*-DBS n=69 incl. retrospective data n=49) (Abbes et al., 2018) 2- **Emotional well-being (PDQ-39)** N=69(Lezcano et al., 2016)*	**1-MADRS** n=16 [control non-DBS PD n=62](Lilleeng et al., 2015) 2-4-**ZAS** N=26(Rizzone et al., 2014)*

Prospective Cohort **Randomized Clinical Trial** **Retrospective** **Consecutive Case Series** **Case-control Study**

	Follow-up Periods					
	3 months	**6 months**	**1 year**	**1-3 years**	**3-6 Years**	**≥6 year**
Worsened	3-**HAM-D+SDS** N=27(Wang et al., 2009) * 4- **STAI** N=31(Chang et al., 2012) 1-**NPI (anxiety)** N=22(Porat et al., 2009)* 2-**HAM-A** (GPi & STN N=30) no difference btw GPi & STN (Okun et al., 2014) * 3- **HAM-D** worsened only in 6/24 patients with preoperative depression(Berney et al., 2002) 4- MINI N= 24 Anxiety and agoraphobia worsened in the first three months and were related to a decrease in antiparkinsonian medication(Houeto et al., 2002)	**2-BDI, HAM-D, YMRS** N=51 *STN*-DBS (Chopra et al., 2014) 3-**HAMD** N=27(Wang et al., 2009)* 1-**GDI** N=6 (Bordini et al., 2007) 2-**HAM-A** + **YMRS** +**HAM-D** (GPi & STN N=30) no difference btw GPi & STN (Okun et al., 2014)* 3_**BDI** (cognitive, emotional items 1-9, 13-15) worsened in the case group (STN-DBS n=17, controlled PD n=22), which was not related to decreases in antiparkinsonian medications (Strutt et al., 2012)	4-**ZAS** N=26(Rizzone et al., 2014)* 5-HAM-A, HAM-D (N=27) (L. L. Jiang et al., 2023)* 1-**STAI+HAM-A** N=31(Chang et al., 2012)* 2-**STAI**+**SRMI** N=27(Lewis et al., 2015) 3-**BDI** N=89(Kim et al., 2013) 41-**GDI** N=6 (Bordini et al., 2007) 5-**HAM-A** + **YMRS** + **HAM-D** (GPi & STN n=30) no difference between GPi & STN (Okun et al., 2014) *	3-1-**BDI + BAI** *STN* N=63(Lhommée et al., 2012) 1-**SDS** N=23(Liu et al., 2021)		3-**BDI** (N=58)(Castrioto et al., 2022) 1-**BDI** N=79 (compared to preop)(Gruber et al., 2019)*

*Table notes: Acronyms column by column: 1-BDI: Beck Depression Inventory, GDI: Geriatric Depression Inventory, BRMES: Bech-Rafaelsen Melancholia Scale, HAM_D: Hamilton Depression Scale, DSD: Depression Scale, STAI: State and Trait Anxiety Inventory, NPI: Neuropsychiatry Inventory, HAM-A: Hamilton Anxiety Scale, MINI: Mini Mental Status Examination, 2- MADRS: Montgomery and Asberg Depression Rating Scale, YMRS: Young Mania Rating Scale, 3-BAI: Beck Anxiety Inventory, SRMI: Self-Report Manic Inventory, ZAS: Zung Anxiety Scale, 4-POMS: Profile of Mood Scale, SDS: Self-Rating Depression Scale, BAS: Brief Anxiety Scale, 5- PDQ-39= Parkinson's Disease Quastionnaire-39 item. 6-BPRS=Brief Psychiatric Rating Scale. * Studies which reported different results at follow-up pe*

SUMMARY POINTS: Predictive Factors for Mood Outcomes < 12 months

- Pre-DBS QoL, tremor severity, sleep quality, psychiatric history and frontal lobe function are potential predictive factors.
- Higher academic degree can potentially predict less improvement.

2.3.3.2.3 Predictive Factors for Post-DBS Mood Outcomes

Ten studies investigated risk factors for exacerbating mood symptoms, alongside new onset mood symptoms, among 668 participants after bilateral STN-DBS therapy (Achey et al., 2018; Birchall et al., 2017; Houeto et al., 2002; Kübler et al., 2023; Perriol et al., 2006; Schadt et al., 2006; Schneider et al., 2010; Strutt et al., 2012; Tir et al., 2007). These findings are summarized in *table* 3. The significant improvement in depression scores among 50 consecutive cases with unilateral STN-DBS was correlated with sleep and quality of life before and six months after the operation (Birchall et al., 2017). A retrospective review of post-DBS outcomes of 203 patients (72% male) revealed improvement in depression scores in males only one year after the operation (Kübler et al., 2023). One-year postoperative *de novo* depressive symptoms (MADRS) were reported to be significantly correlated with a remote history of self-reported depression scores by three studies (Houeto et al., 2002; Perriol et al., 2006; Tir et al., 2007).

Interestingly, in a quasi-experimental setting[9] (N=38), DBS activation led to more significant improvement in participants with preoperative clinically diagnosed depression and anxiety than participants who had preoperative self-reported mood symptoms (Eisenstein et al., 2014). A remote history of depression was also associated with postoperative worsening of depressive symptoms (Berney et al., 2002). A positive relationship was found between baseline immediate recall function and postoperative manic symptoms, as well as the predictive potential of poor performance on tests of frontal lobe function for worsening of post-surgical depressive symptoms (Schneider et al., 2010). An association was also found

[9] The difference between this study design and RCTs lies in their pre-test/post-tests period. Also, they might lack a control group and their criteria for choosing a study group is different.

between pre-operative and postoperative anxiety, which slightly worsened postoperatively in a prospective study (Strutt et al., 2012). In another prospective cohort study, academic attainment (attainment of a degree and higher intelligence test scores) was shown to be associated with less improvement in depression postoperatively (Schadt et al., 2006). Motor symptoms and cognitive function were also reported to have predictive potential. One retrospective study reported that a higher score on patient-rated tremor was a strong predictor of postoperative depression and anxiety (Achey et al., 2018).

Table 5 Risk factors, Predictors and Relation of Mood Symptoms Reported after DBS

	Risk Factors	**Predictors**	**Association**
Depression	-Less benefit of the group with higher educational degrees and higher scores on intelligence tests (Schadt et al., 2006). - History of depression is a risk factor for *De novo* depression (Tir et al., 2007) and worsening (Perriol et al., 2006).	- Preoperative higher self-rated tremor (Perriol et al., 2006; Tir et al., 2007). - Predictive potential of frontal lobe performance, such as verbal fluency for post-surgical depressive symptoms (Schneider et al., 2010).	-Postoperatively not associated with off-state (Witjas et al., 2007). -Postoperatively less associated with disabilities (Witjas et al., 2007). -Associated with negative satisfaction review postoperatively (Maier et al., 2016). - Pre-DBS clinically diagnosed depression showed more significant improvement in comparison to ongoing self-reported mood symptoms (Eisenstein et al., 2014). - Depression scores were correlated with sleep and quality of life before and six months after the operation, when it was significantly improved among 50 consecutive cases with unilateral STN-DBS (Birchall et al., 2017). -Depression ameliorated only among men (72% of N=203) one year after operation (Kübler et al., 2023).
Mania	- Positive relation between baseline immediate recall function and postoperative manic symptoms (Schneider et al., 2010).		-Not associated with negative satisfaction reviews (Maier et al., 2016).
Anxiety/Irritability		A high score in self-rated tremor was identified as a predictor (Tir et al., 2007).	- Postoperatively, it is not associated with off-state rates and disabilities (Witjas et al., 2007). - Pre-DBS clinically diagnosed anxiety showed greater improvement in comparison to ongoing self-reported mood symptoms (Eisenstein et al., 2014).

STN-DBS: Subthalamic Nucleus – Deep Brain Stimulatio

SUMMARY POINTS: Post-DBS Mood Outcome Compared to Alternative Treatment

- Early outcomes are in favour of medical treatment, but not the long-term follow-ups
- Post-DBS irritability is more common than in medical treatment.

2.3.3.2.4 Mood Outcomes After DBS Compared to Alternative Treatment

Thirteen studies evaluated mood outcomes after DBS and other treatments among 573 participants (Castelli et al., 2008; Hacker et al., 2023; Lilleeng et al., 2015; Lule et al., 2012; Mahdavi et al., 2013; Merello et al., 2008; Merola et al., 2014; Pusswald et al., 2019; Smeding et al., 2005, 2006; Straits-Troster et al., 2000; Trepanier et al., 2000; Witt et al., 2008). Medical treatment was favoured in the early postoperative follow-ups (Lule et al., 2012; Smeding et al., 2006; Witt et al., 2008), but later postoperative follow-up was either in favour of DBS treatment (Lilleeng et al., 2015; Smeding et al., 2006) or the difference was negligible (Castelli et al., 2008; Merola et al., 2014; Pusswald et al., 2019; Smeding et al., 2005). A randomised controlled trial revealed that depression was more frequent in the STN-DBS group (n=123) than in the control group (BMT) six months after the intervention (Witt et al., 2008). A higher irritability score was also reported on the Neuropsychiatric Inventory – 12 items among PD-DBS (n=15) participants compared to a matched PD group in an experimental study of the immediate effect of stimulation (Lule et al., 2012). Another case-control (DBS n=99 vs non-DBS PD n=36) reported despite greater improvement in their quality of life, emotional liability on the NPI-12 and positive affect on the Positive and Negative Affect Schedule (PANAS) worsened among the DBS group in the sixth-month follow-up (Smeding et al., 2006). The same study found a slightly better improvement in depression symptoms on the Profile of Mood Scale (POMS) and NPI-12 in favour of the STN-DBS group when compared with the BMT group (Smeding et al., 2006). Consistently, this difference in the improvement of depression (MADRS) among a small DBS group was observed in another long-term prospective cohort study and clinical trial in comparison to a BMT group (N=74) six to eleven years after operation (Hacker et al., 2023; Lilleeng et al., 2015). However, others reported no significant difference between BMT and DBS effects on mood symptoms in the long-term in two case-control studies (N=49) (Mahdavi et al., 2013;

Merola et al., 2014)and a consecutive case series (N=28) (Castelli et al., 2008) with relatively smaller cohorts.

Several studies failed to find any difference between DBS and other modes of treatment over time(Merello et al., 2008; Smeding et al., 2006; Straits-Troster et al., 2000). In one randomised clinical trial (N=19), bilateral STN-DBS and bilateral subthalamotomy caused significant worsening changes in the UPDRS, part one (mood, behaviour and mental activity) twelve months after operation, but not the combination of unilateral subthalamotomy and contralateral subthalamic stimulation (Merello et al., 2008). The authors reported that the score of psychiatric symptoms such as depression on the HAM-D or mania on the Mania Scale MS did not differ between groups over time (Merello et al., 2008). Another RCT reported no difference in depression scores (PONS, MADRS) between bilateral STN (n= 20) and unilateral pallidotomy (n=14) after 12 months (Smeding et al., 2005).

SUMMARY POINTS: Apathy Long-term Outcomes > 12 months

- Apathy reportedly worsens or remain unchanged.
- On non-apathy specific scales, related items showed improvement.

2.3.3.3 Apathy

The direct long-term impact of DBS on apathy varied in seven prospective, two consecutive case series, and two retrospective studies (N=393), mainly between remaining stable (Castelli et al., 2006; Foley et al., 2017; Gruber et al., 2019; Krause et al., 2022; Okun et al., 2014) or worsening (Abbes et al., 2018; Funkiewiez et al., 2004; Kirsch-Darrow et al., 2011; Le Jeune et al., 2009; Maier et al., 2016; Porat et al., 2009). *Table 4* summarizes our findings. Apathy and anhedonia remained stable in two cohort studies (N=49) (Foley et al., 2017; Gruber et al., 2019) and a consecutive case series (no=72) (Castelli et al., 2006) 1-6 years following the operation. On the contrary, a retrospective case-control study reported that apathy increased up to 12 months after DBS operation (STN =33 and GPi =15) (Kirsch-Darrow et al., 2011). The results may be less reliable than long prospective follow-ups due to the retrospective design and smaller cohort. On the other hand, results from earlier follow-up showed significant improvement in the score of items related to apathy. A prospective study (N=60) revealed

improvement in apathy-related items on MADRS, HAMD, and BDI in a 6-month follow-up (Antosik-Wójcińska et al., 2017). Despite the link between apathy and such items, a scale specifically designed for apathy is necessary to produce more reliable results.

SUMMARY POINTS: Post-DBS Apathy Outcome compared to Alternative Treatment

- The comparison to other modes of treatment, including medical treatment, apomorphine, revealed no difference in short-term.
- In the long-term, Apathy is more common after STN-DBS.

2.3.3.3.1 Apathy Outcomes of DBS in Comparison to Alternative Treatments

Post-DBS outcomes of apathy are compared to other treatments by four studies, including three RCTs and one retrospective study, among 183 participants (Antonini et al., 2011; Fisher et al., 2016; Lhommée et al., 2018; Merello et al., 2008). *Table 4* summarizes our findings. *Figure 7 and 8* visualize frequency of the reported effect and their follow-up timeline, respectively. Comparing DBS effect on apathy scores to other modes of treatment, including medical treatment, apomorphine, and other surgical approaches, revealed no difference (Fisher et al., 2016; Lhommée et al., 2018; Merello et al., 2008) or worse outcomes for DBS (Antonini et al., 2011). A secondary analysis in an open-label RCT of the STN-DBS + medical treatment group (n=124) *vs.* the BMT group (n=127) revealed that apathy remained unchanged in both groups up to two years postoperatively (Lhommée et al., 2018). Another small non-RCT (STN n=13, apomorphine n=12) reported that apathy (AS) worsened significantly only among STN patients one year after the operation (Antonini et al., 2011). Retrospective designs produced less reliable results because the authors could not investigate if a change in apathy in the DBS group resulted from stimulation due to a lack of baseline data (Fisher et al., 2016). Instead, they could only evaluate apathy scores at a certain point after the DBS operation and compare them to a control group.

2.3.3.3.2 Predictive Factors for Post-DBS Apathy Outcomes

Risk factors for developing apathy have been investigated in seventeen studies, including 536 participants (Maier et al., 2016).

- *Preoperatively*, a 'hyperdopaminergic' profile (Lhommée et al., 2012)(Santin et al., 2021), higher self-rated depression score (Denheyer et al., 2009), age above 65 (Kirsch-Darrow et al., 2011), higher UPDRS III motor scores on L-dopa (Gesquière-Dando et al., 2015), longer disease duration (Gesquière-Dando et al., 2015), lower motor-dopa sensitivity (Gesquière-Dando et al., 2015) and dyskinesia (Higuchi et al., 2015) were reported to be significantly associated with postoperative apathy.
- *Postoperatively*, higher postoperative reduction in dopaminergic medications (Denheyer et al., 2009), age above 65 (Kirsch-Darrow et al., 2011), less improvement in depression and anxiety (Maier et al., 2016; Martinez-Fernandez et al., 2016; Thobois et al., 2010), impairment in executive dysfunction (except verbal fluency) (Denheyer et al., 2009) and reduced glucose metabolism in bilateral cingulate and left middle frontal gyrus (Le Jeune et al., 2009) were found to be significantly associated with worsening of apathy.
- Preoperative apathy was also reported to have a predictive potential for postoperative poor satisfaction with the DBS results (Maier et al., 2016), less motor improvement (Maier et al., 2016) and a lower LEDD reduction rate (Denheyer et al., 2009). *Table 4* summarizes our findings.

Our results on potential predictive factors of postoperative apathy include various study designs with a common characteristic of small cohorts ranging from 15 to 63 participants. Despite being insightful for future work, these results are unreliable due to the cohort size, and replication in larger cohorts will be required (Drapier et al., 2006; Kirsch-Darrow et al., 2011). In addition, three prospective studies and three consecutive case series with similar cohort sizes failed to find such an association between postoperative apathy and mood symptoms, DBS parameters, preoperative LEDD, cognitive function (Castelli et al., 2006; Foley et al., 2017; Gesquière-Dando et al., 2015; Thobois et al., 2010), changes in LEDD (Le Jeune et al., 2009), or UPDRS scores (Thobois et al., 2010)(Kirsch-Darrow et al., 2011). The relationship of mood symptoms with apathy is complex, as depression is not consistently associated with postoperative apathy. In one consecutive case series (Drapier et al., 2008), one prospective cohort (Porat et al., 2009) and one randomised pilot study (Merello et al., 2008), the authors reported worsening of apathy and anxiety postoperatively without finding

any significant change in depression (N=56). Lastly, the relationship between apathy and cognitive dysfunction has also been explored. Postoperative apathy was found to be associated with postoperative executive dysfunction, except for verbal fluency, which is partially supported by two more studies (Denheyer et al., 2009). Using the self-rating apathy scale (AES) and the clinician-rated UPDRS - Part I, two consecutive case series (N=90) reported that postoperative apathy did not correlate with a decline in verbal fluency after DBS (Castelli et al., 2006; Foley et al., 2017).

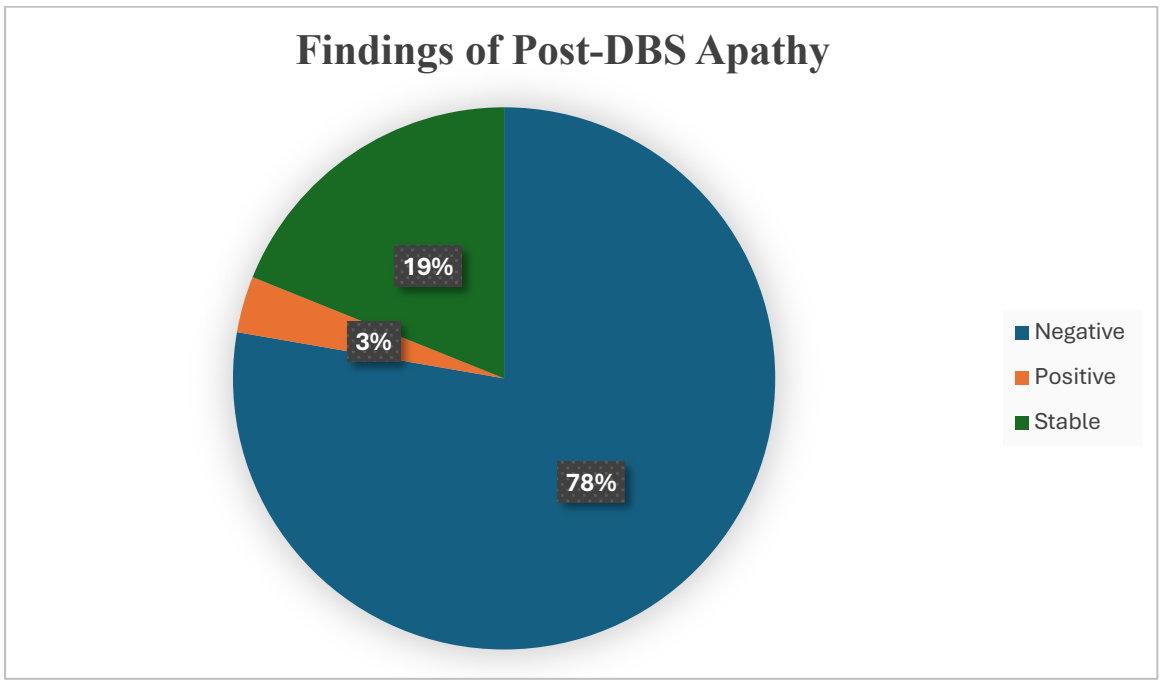


Figure 7 Findings of Post-DBS Apathy

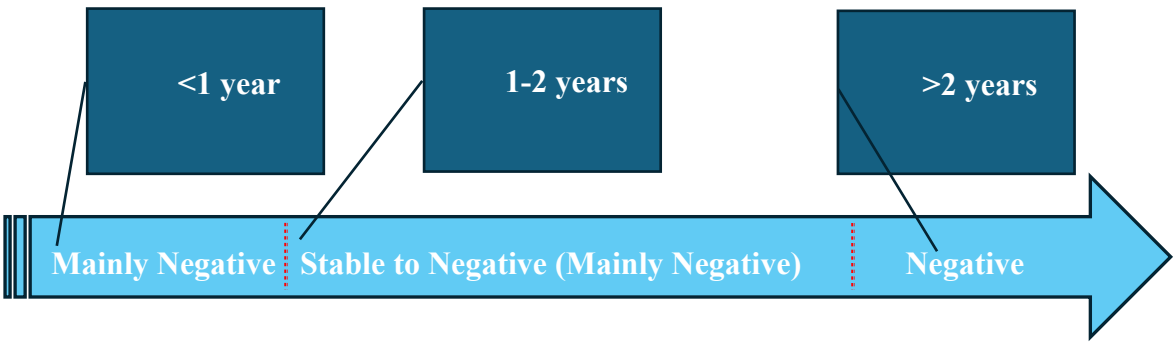


Figure 8 DBS effect on Apathy on a Follow-up Timeline

Table 6 Effects of DBS on Apathy, Correlation with Other Outcomes and Comparison with Other Treatment

	DESIGN	N=	FOLLOW-UP DURATION	OUTCOME	FINDINGS
Jeune et al, 2009	Prospective cohort study	12	3 months	Negative	-Apathy on the AES **significantly worsened.**
Boon et al, 2021	Prospective cohort study	26	6 months	Negative	Apathy **significantly worsened** following DBS.
Kirsch-Darrow et al, 2011	Prospective cohort study	Uni STN n=33 Uni GPi n=15	6 months	Negative	-Apathy on the AS **significantly worsened** over time (6 months) in all DBS cases. -STN and GPi groups were not compared.
Maier et al, 2016	Prospective cohort study	28	12 months	Negative	-Apathy **significantly worsened** over time on the AES.
Funkiewiez et al, 2004	Consecutive case series	77	12 months	Negative	-Apathy **significantly worsened** on the UPDRS I (item 4).
Merello et al, 2008	RCT *	15 (5 in each arm)	12 months	Negative	-Apathy **worsened non-significantly** after 12 months postoperatively.
Okun et al, 2014	RCT	STN n=16	12 months	Negative	-Apathy **worsened non-significantly** on the AS in both stimulation targets 12 months after operation.

	DESIGN	N=	FOLLOW-UP DURATION	OUTCOME	FINDINGS
		GPi n=14			-No difference between the two stimulation targets over time.
Lhommee et al, 2018	Open labelled RCT	STN n=124	24 months	Negative	Apathy **worsened non-significantly** on the SAS when STN-DBS + medical treatment was combined.
Porat et al. 2009	Prospective cohort study	25	24 months	Negative	-Apathy **significantly worsened** on the NPI over time -5 cases had *de novo* apathy postoperatively.
Krack et al, 2003	Consecutive case series	42	5 years	Negative	-In 5 patients out of 42, apathy diagnosed by Marin criteria[10] **became permanent,** but the effect of DBS was not tested. -All transient apathy (2 out 42) responded to either antidepressant dopamine or both.
Abbes et al 2018	Prospective and retrospective cohort study	69	3-10 years	Negative	-Apathy on the SAS **significantly worsened.**
Castelli 2006	Consecutive case series	72	15 months	Stable	Apathy on UPDRS I (item 4) was **unchanged** over time.
Foley et al., 2019	Consecutive case series	28	19 months	Stable	Apathy was **unchanged.**

[10] Marin "lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress."(207)

	DESIGN	N=	FOLLOW-UP DURATION	OUTCOME	FINDINGS
Gruber et al 2019	Retrospective cohort study	20	6 years	Stable	Apathy was **unchanged** on the SHAPS-D.
Antosik-Wójcińska et al. 2017	Prospective cohort study	46	6 months	Positive	-Apathy significantly **improved** on the SHAPS and selected apathy subscores on MADRS, HADS and BDI
			Comparing effects of DBS vs. other treatments on apathy		
Fisher et al., 2016	Retrospective, Case-control	STN n=22 Medically treated PD n=38	48 months	**-Found no difference** in the prevalence of apathy on the LARS and the AS between DBS patients and a matched medically treated PD group. _Effect of DBS on apathy was not investigated.	
Lhommee et al, 2016	Open labelled RCT	STN-DBS + MT n= 124 MT PD n=127	24 months	-**The two groups did not differ** in apathy scores (SAS).	
Merello et al, 2008	RCT	15	12 months	- Apathy on the AS was **more stable in bilateral STN** and a combination of unilateral STN and unilateral subthalamotomy treatment than in the bilateral lesion group.	

	DESIGN	N=	FOLLOW-UP DURATION	OUTCOME	FINDINGS
Apathy associations with motor, cognitive and psychiatric symptoms					
Drapier et al, 2006	Prospective cohort study	26	6 months	-Worsening of apathy was not correlated with motor scores, medication reduction or mood changes.	
Denheyer et al, 2019	Retrospective cohort study	16	12 months	-Apathy subscores were found to be correlated with executive dysfunction (FrSBe). - Apathy was positively correlated to the higher reduction in dopaminergic dosage and high self-rated depressive symptoms after the operation.	
Jeune et al, 2009	Prospective cohort study	12	3 months	-Increased apathy (poor performance) was negatively associated with reduced glucose metabolism in the bilateral cingulate and left middle frontal gyrus.	
Foley et al., 2017	Consecutive case series	28	19 months	Apathy on the Apathy Evaluation Scale was preoperatively correlated with the postoperative decline in verbal fluency, but postoperative apathy was not correlated with the postoperative decline in verbal fluency.	
Castelli et al, 2006	Consecutive case series	72	15 months	Apathy on UPDRS I (item 4) was not correlated with the postoperative decline in verbal fluency.	
Kirch-Darrow et al, 2011	Prospective cohort study	Uni STN n=33 Uni GPi n=15	6 months	-Postoperative Apathy on AES was positively correlated to age <65 – More affected in middle aged. -Preoperative depression did not predict postoperative apathy. -Apathy was not associated with contact location and laterality.	

	DESIGN	N=	FOLLOW-UP DURATION	OUTCOME	FINDINGS
					-Failed to find predictive values for apathy in baseline depression, change in LEDD, or UPDRS scores.
Robert et al., 2014	Prospective cohort study	44	3 months		-Postoperative apathy is strongly associated with the preoperative change in metabolism in a vital part of the limbic system and reward circuitry, the right ventral striatum.
Higuchi et al, 2015	Consecutive case series	25	1 month		-Preoperative dyskinesia was found to be an independent predictor of post-DBS apathy.
Thobois et al, 2010	Prospective cohort study	62	12 months		-Baseline anxiety scores and non-motor symptom fluctuation are found to be independent predictors for post-DBS apathy on the SAS.

*Table notes: *The RCT had three arms: bilateral DBS, unilateral DBS/unilateral subthalamotomy, and bilateral subthalamotomy. Acronyms: AES: Apathy Evaluation Scale, AS: Apathy Scale, SAS; Starkstein Apathy Scale, SHAPS-D: Snaith-Hamilton-Pleasure-Scale, HADS: Hospital Anxiety and Depression Scale, LARS: Lille apathy rating scale, FrSBe: Frontal Systems Behavior Scale, DBS: Deep Brain Stimulation. GPi: Globus Pallidum interna*

SUMMARY POINTS: Long-term Effects on ICBs > 12 months

- Long-term effects are reportedly promising.
- Individual ICBs respond differently.
- The prevalence of *De novo* cases are not uncommon at 8-15%.

2.3.3.4 Impulse Control Behaviours

The effect of DBS on impulse control behaviours (ICBs) varies between individual ICB types (Abbes et al., 2018; Kim et al., 2013) as well as postoperative duration (Abbes et al., 2018; Gee et al., 2015; Somma et al., 2022). Several studies, including a non-randomized clinical trial (Rossi et al., 2017), retrospective study (Kim et al., 2013), experimental study (Eusebio et al., 2013), a prospective and retrospective study (Abbes et al., 2018) and five consecutive case series (Ardouin et al., 2006; Eusebio et al., 2013; Gee et al., 2015; Merola et al., 2017; Pham et al., 2015) reported a significant decline in ICBs-related symptoms up to 12 months following the operation. In a 6–12-month non-RCT (N=32), the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) scores reportedly declined among patients with ICBs after receiving GPi- (n = 23) and STN-DBS (n = 14) (Rossi et al., 2017).

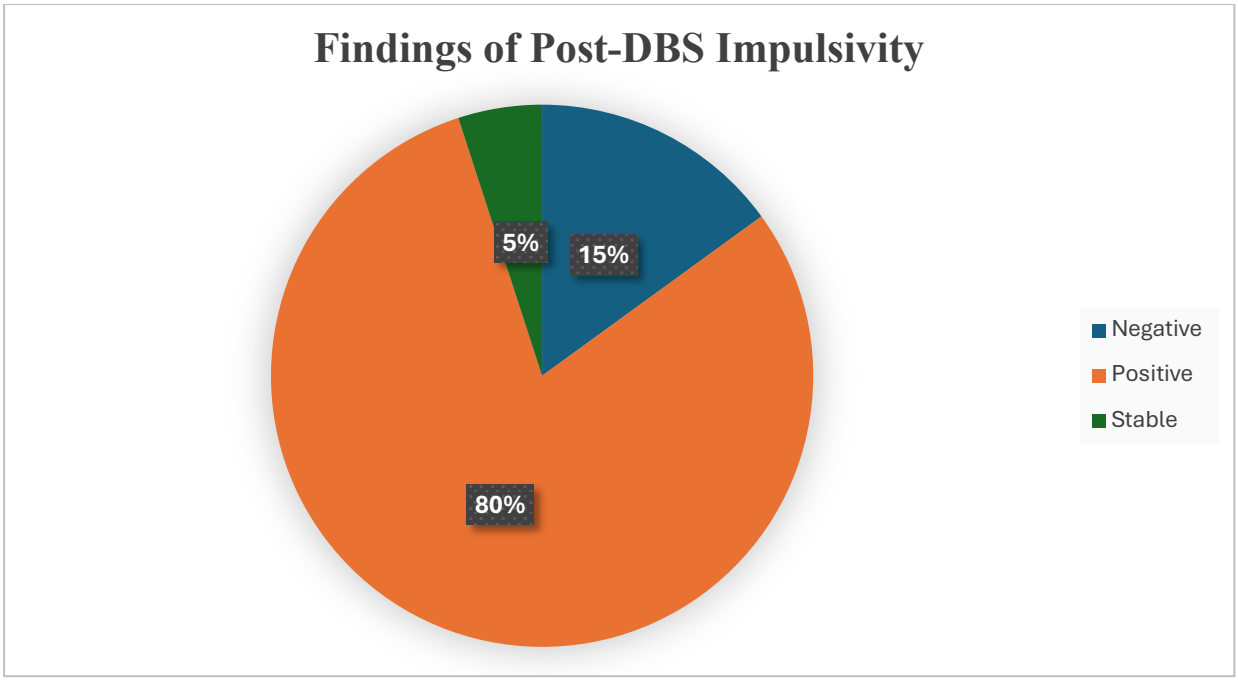


Figure 9 Findings of Post-DBS Impulsivity

Of note, not all impulsive behaviours were affected similarly. The authors of a retrospective study reported that gambling had the best response to STN-DBS with no *de novo* cases up to three years after operation (Kim et al., 2013). Hypersexuality and binge eating were reduced in most patients with ICBs (QUIP-RS) over 12 months postoperatively in a consecutive case series (N=16) (Gee et al., 2015). However, 3-10 years after the operation, hypersexuality and excessive eating were not among 'hyperdopaminergic' behaviours that were reduced on the Ardouin scale in a prospective and retrospective cohort study (N=69) (Abbes et al., 2018).

In a retrospective review of a smaller cohort (N=22), others reported worsening of ICDs among 22% of participants with significant socioeconomic outcomes (Şimşek Erdem et al., 2023). However, these participants were one decade younger at one-year follow-up than those who reported improvement 3-10 years after the operation (Şimşek Erdem et al., 2023). A case-control study suggested that STN-DBS may increase impulsivity by enhancing automated response to reward (Eisinger et al., 2020). The authors measured impulsivity in a reward-based go/no-go to investigate the effect of STN-DBS on Pavlovian biases[11].

Regarding *de novo* ICBs, the prevalence is reported at 8-15% in a non-RCT (unilateral GPi, SNT DBS N=37) (Rossi et al., 2017), two retrospective studies (N=89 and N=137) (Healy et al., 2022; Kim et al., 2013), two prospective studies (N=37) (Hernandez-Con et al., 2023; Schupbach et al., 2005) and a cross-sectional study (N=17) (Tsai et al., 2013) one to three years after the operation. Moreover, a relapse of resolved impulsive behaviours was also reported immediately after the operation. In a cohort of ninety-nine patients who underwent DBS, the authors retrospectively reported 1% relapse of voyeurism and 1% pathological gambling (Smeding et al., 2006).

Lastly, the effects of STN-DBS were compared to dopamine agonist DA in two experimental studies; STN-DBS was shown to have a less immediate effect on impulsivity and PD patients on DA-only made less rational decisions (Lees et al., 2013; Lule et al., 2012)[12]. Consistently, an open-labelled randomized clinical trial found that hobbyism and hyperdopaminergic behaviours (Ardouin scale) increased in patients treated with medication only, whereas it improved in patients receiving DBS and medical treatment two years after the operation (Lhommee et al., 2017). However, the authors of a prospective control study found no

[11] Pavlovian bias indicates that reward-related cues boost action (lead to more active "Go" responses) whereas punishment-related cues restrain action.

[12] Beads task and Gambling task (Lees et al., 2013; Lule et al., 2012).

significant differences between the two groups one year after the operation (DBS n=26 vs. control n=28) (Hernandez-Con et al., 2023).

SUMMARY POINTS: Predictive Factors for ICBs outcome < 12 months

- Individual ICBs can have distinct predictive factors.
- Personality traits, reduction in DRT, younger age predicted improvement.
- Gender and psychiatric outcomes are predictive of impulsivity in general.
- De novo cases of ICBs are common.
- There are conflicting results about relation between personality traits and impulsivity post-DBS.
- There are conflicting results about relation between DA use and impulsivity post-DBS.

2.3.3.4.1 Predictive Factors for ICB Outcomes

Predictive factors for outcomes related to ICBs, including gambling and DDS, have been identified as preoperative personality traits (Hernandez-Con et al., 2023; Pham et al., 2015), reduction of dopaminergic (Kim et al., 2013; Lhommée et al., 2018; Lule et al., 2012; Rossi et al., 2017), younger age (Janssen et al., 2014), gender (Abbes et al., 2018; Kim et al., 2013; Kübler et al., 2023), psychiatric comorbidity (Eisinger et al., 2022; Kim et al., 2013; Merola et al., 2017) and contact location in STN (Somma et al., 2022). A retrospective study (N=89) and two consecutive case series studies (N=150, N=539) reported that impulsivity reduced concomitantly with a postoperative dopaminergic reduction among patients with a history of gambling and DDS at baseline (Ardouin et al., 2006; Kim et al., 2013; Merola et al., 2017). However, a consecutive case-series suggested that DBS may have led to new stereotyped behaviours, differentiated by a strong appeal towards punding, a complex, non-goal-oriented, repetitive activities behaviour, as the authors found no difference in DBS-induced reduction in dopamine agonists (DA) between punders and non-punders (Pallanti et al., 2010). The authors, however, did not report whether the punders were positive for ICBs before the operation. Consistently, DA use was not reduced in all patients whose impulsivity improved

post-GPi- and STN-DBS, and patients with postoperative ICBs did not show statistically significant higher LEDD (Rossi et al., 2017).

Moreover, *de novo* hypersexuality and eating disorders were reported predominantly among men (Kim et al., 2013) and women (Abbes et al., 2018.), respectively. Higher preoperative LEDD (Kim et al., 2018) and longer PD duration (Healy et al., 2022) were also correlated with *de novo* ICBs. A long-term retrospective study (N=150) found that preoperative ICBs reported in clinical diagnostic interviews (N=26) showed no association with personality traits (SCID-II). However, persistent ICBs were reported to be associated with obsessive-compulsive traits and *de novo* ICBs with borderline, schizoid and schizotypal personality traits (Merola et al., 2017). In addition, *de novo* ICD was significantly associated with baseline apathy scores, according to a prospective study (N=217) (Santin et al., 2021), a relation that needs further investigation. Certain personality traits, such as high novelty seeking and avoidance of harm, may expedite these effects (Pham et al., 2015). In addition, the severity of ICBs was inversely correlated with changes in the BDI after DBS operation (Kim et al., 2013; Merola et al., 2017). Of interest, postoperative ICBs, which were reported by patients and carers at follow-up several years after the operation, were not related to response inhibition measured by the Stroop colour-word test at baseline (Janssen et al., 2014).

Table 7 Summary of Reports on the Effect of DBS on Impulsivity

Study	Study design	N=	Measuring tool	Summary of reports on the effect of DBS on Impulsivity		
				Result		
				Overall	**Improved/worsened/Stable**	***De novo.***
Rossi et, 2017	non-RCT	GPi n=23 STN n=14	QUIP	- DA did not reduce in all patients whose impulsivity improved post-GPi and STN DBS - Patients with postoperative ICBs did not show statistically significant higher LEDD. - LEDD was not correlated with MIDI scores among preoperative and postoperative ICB + patients.	-Impulsivity improved on the QUIP 6-12 months postoperatively. - 7/14 patients with preoperative ICBs no longer met the criteria for ICB diagnosis postoperatively.	- *De novo* impulsive behaviours occur 12 months after the unilateral STN-DBS and GPi-DBS operation at 10.8%.
Santin et al, 2021	Prospective cohort study	217		-10% of the cohort had an ICD at baseline.	-95% of positive cases of ICD improved.	-There were 3% *de novo* cases of ICD. -Those with *de novo* ICD had higher apathy scores at baseline.
Kim et al, 2013	Retrospective cohort study	89	Modified MIDI (ex. DDS) + medical notes	- Older age at the time of DBS or PD diagnosis was shown to be associated with the preoperative MIDI scores but not postoperatively.	-ICBs improved in 13 out of 20 preoperative ICBs + 6-12 months after operation. -Gambling had the best response, with complete resolution in all cases and did not have any *de novo* cases.	-*De novo* ICBs were reported among 9 patients 1-3 years postoperation (20/89 patients had ICBs before DBS).

Study	Study design	N=	Measuring tool	Summary of reports on the effect of DBS on Impulsivity		
				Result		
				Overall	Improved/worsened/Stable	*De novo.*
Lule et al, 2012	Experimental study	15	PC-based IOWA gambling task		- Immediate attenuating effect of stimulation on gambling measured by PC-based IOWA gambling task during ON stimulation. -PD patients on high doses of medication made more disadvantageous decisions.	
Abbes et al, 2018	Prospective and retrospective cohort study	69	Ardouin scale		- Hyperdopaminergic behaviours, including impulsive behaviours except for hypersexuality and excessive eating, were reduced 3-10 years after the operation.	
Gee et al, 2015	Prospective cohort study	16	QUIP-RS		- Reduction of hypersexuality and binge eating in the majority of patients with ICBs one year after receiving STN-DBS.	
Somma 2022	Prospective Cohort Study (Nonconsecutively case series)	14	BIS-II		-Worsening in motor, no planning and **attentional** impulsivity 12 months after the operation, which was significant only for the latter.	

Study	Study design	N=	Measuring tool	Summary of reports on the effect of DBS on Impulsivity		
				Result		
				Overall	Improved/worsened/Stable	*De novo.*
Eusebio et al, 2013	Consecutive case series cohort study	110	MIDI		-Except for one patient, all others (n=17) with compulsive dopamine showed a significant reduction and reported no *de novo* cases. -90% of patients with compulsive dopamine use had at least one ICB that has also improved.	
Merola et al, 2017	Consecutive case series	150	clinical diagnostic interview	-ICBs severities were inversely correlated with changes in BDI after DBS operation. -Postop persistent ICBs and *de novo* ICBs were reported to be associated with obsessive-compulsive and borderline, schizoid and schizotypal personality traits (SCID-II), respectively.	-The prevalence of ICBs showed a reduction trend in 18 out of 26 patients with ICBs 8-60 months postoperatively. -ICBs persisted in 8 out of 26 patients 11-82 months postoperatively.	-11 Out of 150 participants developed *de novo* ICBs 6-84 months postoperatively, and 5 out of 11 developed multiple ICBs.
Ardouin et al. 2006	Retrospective cohort study	598	Clinical diagnosis of pathological gambling PG (DSM IV)		-7 patients had active PG at the time of operation. -All 7 patients developed PG 1-8 years after being on dopamine replacement therapy. -Pathological gambling symptoms resolved in parallel to dopamine dose reduction 2-6 years after operation.	-

Study	Study design	N=	Measuring tool	Summary of reports on the effect of DBS on Impulsivity		
				Result		
				Overall	Improved/worsened/Stable	*De novo.*
					- Persistent PG was reported in a more controlled fashion and did not meet the diagnostic criteria	
Pallanti et al, 2010	Consecutive case series	24	An adapted version of 26 item-questionnaire used by Evans and colleagues	-5 punders were recognised out of 24 patients surveyed after the DBS operation. - No difference was found in postoperative DBS-induced reduction in dopamine agonists between punders and non-punders.		
Janssen et al, 2014	Prospective cohort study	26	Self-reported and carer-reported Behavioural changes documented	- Postoperative impulsivity (9/26) was trending towards younger age -No information given on pre-operative ICBs -Postoperative ICBs reported by patients and carers at follow-up several years after		

Study	Study design	N=	Measuring tool	Summary of reports on the effect of DBS on Impulsivity		
				Result		
				Overall	**Improved/worsened/Stable**	***De novo.***
			during follow-up	the operation were unrelated to inhibition measured by the Stroop colour-word test.		
Kim et al, 2018	Further follow-up of 61 out of 89 patients from their previous study (125)	61	MIDI	-8/61 patients reviewed had ICB before the operation whose ICBs resolved after 7 years.		-7 out of 61 had *de novo* ICBs 7 years after operation. -Do novo ICB patients had a greater reduction in their DA than non-ICB patients.

SCID-II: The Structured Clinical Interview for DSM-IV Personality Disorders, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, SCL-90-R: The Symptom Checklist-90-Revised, RT: Rorschach test, ISPC: Iowa Scales of Personality Change, STN-DBS: Subthalamic Nucleus Deep Brain Stimulation, BDI: Beck's Depression Inventory, ICB: Impulsive-Compulsive Behaviours, LEDD: Levodopa Equivalent Daily Dose, PG: Pathological Gambling, MIDI: Minnesota Impulse Disorders Interview, DDS: Dopamine Dysregulation Syndrome, RCT: Randomised Clinical Trial.

Table 8 Summary of Reports on Comparing the Effects of DBS on Impulsivity with Other Treatments

			Comparing DBS effects on ICBs to other treatments		
				The comparing groups	**Results**
Kim et al, 2018	Experimental study	11	Beads Task	-L-Dopa monotherapy -L-Dopa + DA -STN-DBS + L-Dopa -(compared healthy population)	-DA was associated with irrational decisions and impulsivity, not the DBS.
Lees et al, 2013	Experimental study	15	PC-based IOWA gambling task	- PD-DA only -PD STN-DBS	-STN-DBS was shown to have a less immediate effect on impulsivity. -PD-DA had a poorer performance on the Gambling task.
Lhommee et al, 2018	Open-label RCT	17	Ardouin Scale	-PD-medical therapy -PD-DBS + medical therapy	- Hobbyism and hyperdopaminergic behaviours increased in patients treated with medication only, whereas it improved in patients receiving DBS and medical treatment after two years.

DA: Dopamine Agonist, STN-DBS: Subthalamic Nucleus Deep Brain Stimulation, PD: Parkinson's Disease, IOWA: Iowa Scales of Personality

SUMMARY POINTS: DBS effects on Personality Traits

- Variably Notable changes have been observed in personality traits, by informant and patients.
- Personality traits including extravagance, harm avoidance, persistence are reportedly improved following DBS.
- The variability of tools which were used to measure traits is the main issue in the reviewed studies.

2.3.3.5 Personality Traits

Several studies have used various qualitative and quantitative instruments to investigate the effects of DBS on personality traits. Most of the included studies reported notable changes in personality traits after up to three years following the operation(Castelli et al., 2006; Houeto et al., 2002; Lewis et al., 2015; Lhommee et al., 2017; Pham et al., 2015, 2021). Others reported no change in personality traits up to 24 months postoperatively (Castelli et al., 2006; Houeto et al., 2006; Perozzo et al., 2001). Apart from the study designs, assessment tools are another major difference between all these studies. Moreover, the various rating agencies can produce results that are significantly different. For example, in a prospective study (n = 27), 43% of caregivers believed patients' personality had changed, but only 22% of patients reported that (Lewis et al., 2015). The change, whether an increase or a decrease, can also vary across domains and traits, with varying significance. Personality traits that have been repeatedly reported to change after DBS include extravagance and harm avoidance (Lewis et al., 2015; Lhommee et al., 2017; Merner et al., 2023), obsessive-compulsive trait (Castelli et al., 2006) and persistence (Lewis et al., 2015). The authors of a prospective cohort study (N=73) investigated changes in personality after STN-DBS using the Tridimensional Personality Questionnaire (TPQ). Scores on subdimensions of extravagance, harm avoidance, shyness, anticipatory worry, and fatigability significantly reduced 12 months after the operation, whereas other subdimensions remained unchanged (Lhommee et al., 2017). A further three-year follow-up (n = 25) versus a matched control group revealed a significant reduction in scores for obsessive-compulsive trait on the semi-structured Clinical Interview for the DSM-III-R Axis II Disorders (SCID-II) (Castelli et al., 2006).

Furthermore, a consecutive case series study (N=62) reported a significant reduction in scores on obsessive-compulsive and paranoid personality traits[13] 15 months after the operation (Castelli et al., 2006). On the other hand, a prospective study of 40 patients showed a significant drop in scores in persistence, self-transcendence [14] and lack of premeditation[15] with no change in the Eysenck Personality Questionnaire (EPQ) three months after STN-DBS (Pham et al., 2015). However, two prospective studies reported no change in Temperaments and Character Inventory–Revised (TCI-R) scores 6-24 months after receiving DBS (Houeto et al., 2006; Perozzo et al., 2001). As well, using a projective personality test, the Rorschach (RT) test, others in a consecutive case study (N=40) reported stable personality indices one year after the operation (Castelli et al., 2006). Regarding the significance of personality traits, in a prospective study (N=27), the preoperative hypomanic trait [16] was a strong predictor of self-reported changes in personality following STN-DBS one year after the operation (Lewis et al., 2015). The authors of a prospective 12-month follow-up reported positive correlations between scores of personality dimensions on the TPQ, fluctuation in psychiatric severity, and also between postoperative shyness subdimension of harm avoidance and reduction in post-op total levodopa equivalent dose (LED) (Lhommee et al., 2017)

[13] This is measured by the Structured Clinical Interview for DSM-IV (SCID-II) (Castelli et al., 2006).

[14] This is measured by Temperament and Character Inventory (TCI) (Pham et al., 2015a).

[15] This is measured on the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behaviour Scale (the UPPS impulsive behaviour scale) (Pham et al., 2015a)

[16] This is measured using the hypomanic personality scale, HPS (Lewis et al., 2015).

Table 9 Summary of Findings of DBS Effect on Personality Traits (Arranged First by Outcomes [Improved -Stabilized- Declined], Then by Duration of Follow-Up

	Design	**No**	**Follow-up duration**	**Tool**	**Result**
Lhommee et al, 2017	Prospective Cohort Study	73	12 months	TPQ	- Significant increase in scores for harm avoidance HA dimension -No change in novelty seeking (NS) dimension and reward dependent (RD) global score. - Significant drop in scores for Extravagance subdimension NS and persistence dimension PD scores and Shyness.
Seijo Zazo et, 2018	Prospective cohort study	30	12 months	Y-BOCS	-Significant improvement in obsessive-compulsive behaviours.
Castelli et al, 2006	Consecutive Case series	62	15 months	SCID-II	The Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II). Significant improvement in obsessive-compulsive and paranoid personality trait.
Kaiser et al, 2008	Prospective cohort study	33	36 months	SCL-90-R	On the Symptom Checklist-90-Revised (SCL-90-R), obsessive-compulsive symptoms and interpersonal sensitivity declined up to one year after the operation but eventually returned to baseline.
Lewis et al., 2015	Consecutive Case series	27	12 months	Semi-structured interviews	Caregivers reported personality changes more frequently.
Perozzo et al, 2001	Prospective cohort study	15	6 months	SCID II	No change was observed.
Castelli et al., 2006a	Consecutive Case series	40	12 months	RT	Personality traits were stable after one year.

	Design	No	Follow-up duration	Tool	Result
Houeto et al, 2002	Retrospective Study	26	17 months	ISPC	The ISPC Showed either improvement or stability of personality traits among 2/3 of the participants.
Houeto et al, 2006	Prospective cohort study	15	24 months	TCI-R	No change was observed.
Pham et al., 2015	Prospective cohort study	40	3 months	TCI, EPQ, UPPS	Significant deterioration in persistence, self-transcendence (TCI), and lack of premeditation (UPPS impulsive behaviour scale) were observed, but not the Eysenck Personality Questionnaire.
Merner et al, 2023	Retrospective Qualitative study	8	1 year	Interview	80% reported personality-related benefits after STN-DBS.

TPQ: Tridimensional Personality Questionnaire, Y-BOCS: Yale-Brown Obsessive Compulsive Scale, SCID-II: The Structured Clinical Interview for DSM-IV Personality Disorders, SCL-90-R: The Symptom Checklist-90-Revised, RT: Rorschach test, ISPC: Iowa Scales of Personality Change, TCI: Temperaments and Character Inventory, TCI-R: Temperaments and Character Inventory–Revised, EPQ: Eysenck Personality Questionnaire, UPPS: Urgency, Perseverance (lack of), Premeditation (Lack of) and Sensitivity seeking (Lack of). STN-DBS: Subthalamic Nucleus Deep Brain Stimulation

SUMMARY POINTS: DBS Effect on Suicidality

- Suicidality include suicidal ideations to completion.
- Suicidality has been reported at 0.45% to 31%.
- Suicide completion is rare, but slight above the general population.
- Being single, having a history of obsessive-compulsive disorder, previous suicide attempt and impulsivity are suggested to be the risk factor.

2.3.3.6 Suicidality

Fourteen studies reported suicidality at rates of between 0.45% to 31% (Abbes et al., 2018; Castelli et al., 2006; Funkiewiez et al., 2004; Gervais-Bernard et al., 2009; Giannini et al., 2019; Houeto et al., 2002; Kennis et al., 2023; Krack et al., 2003; Porat et al., 2009; Seijo Zazo et al., 2018; Soulas et al., 2008; Tir et al., 2007; Vitek, et al., 2020; Voon et al., 2008; Weintraub et al., 2013). In a large multicentre retrospective study (N=5311), the authors estimated the rates of completed and uncompleted suicide over a mean period of 6 years were 0.45% and 0.9%, respectively (Voon et al., 2008). A randomized, double-blind clinical trial (STN n=121 *vs.* subtherapeutic STN n=39) reported *de novo* mild suicidal ideation on the Columbia-Suicide Severity Rating Scale (C-SSRS) among 3% of patients receiving active STN-DBS in comparison to none among the control group (receiving subtherapeutic SNT-DBS) three months after operation (Vitek, et al., 2020). Of note, a continuous significant deterioration of ongoing suicide risk on the Brief Psychiatric Rating Scale (BPRS), suicide subscale, and the Beck Scale for Suicidal Ideation (SSI) were reported by two prospective cohort studies and one retrospective study (Porat et al., 2009; Seijo Zazo et al., 2018; Voon et al., 2008). Furthermore, suicide may occur several months after the operations, as one participant (1.2%) completed suicide 36 months postoperatively in a consecutive case study (N=77) (Funkiewiez et al., 2004). When compared to national data in long-term follow-up studies, suicide completion and attempts were also higher three to ten years after the DBS operation (Abbes et al., 2018; Giannini et al., 2019). Of note, the observed 10% positive suicidal ideation (item 9 on BDI) in the 15-month follow-up did not meet the indicative score

(>3) of the risk of a suicidal attempt in another prospective study (N=65) (Castelli et al., 2006). The suicide rate after the DBS operation was also compared with that of alternative therapies and control groups. A retrospective review of a large cohort (N=11,390) of PD-DBS found a significantly lower risk for suicidality in comparison to a matched control cohort (N=11,390) of PD without the DBS group (Kennis et al., 2023). In addition, a randomised control trial (N=255) found no significant relation between DBS and suicidality compared to BMT patients (Weintraub et al., 2013).

Some studies investigated suicide risk factors following DBS. Three retrospective studies, two prospective and consecutive case series studies found that attempted suicide was strongly associated with being single, having a history of obsessive-compulsive disorder (Krack et al., 2003) and previous suicide attempt (Krack et al., 2003; Porat et al., 2009), postoperative depression (Soulas et al., 2008; Voon et al., 2008), preoperative depression (Houeto et al., 2002; Tir et al., 2007), and impulsivity (Soulas et al., 2008).

Table 10 Summary of Reports on the Effect of DBS on Suicidality

	Design	No	Tool	Results
Voon et al. 2008	Multicentre Retrospective case-control Study	5311	Chart review	The rate of completed and incomplete suicide is 0.45% and 0.9%. Three completed and three incomplete suicide attempts were recorded among patients who were on the waiting list.
Abbes et al. 2018	Prospective (and retrospective) cohort study	69	Review Charts + Ardouin Scale of Behaviour in Parkinson's Disease	-Suicide attempts in weeks after operation in one and year after operation in three patients. -No completed suicide reported. -Suicide attempt rate was 5.8% at 10-year follow-up. The risk of suicide increased significantly when measured 10 years after the operation.
Porat et al. 2009	Prospective cohort	22	BPRS	Using BPRS, the study found that 1 out of 22 patients attempted suicide 1 month after the operation and completed suicide 3 months after the operation.
Giannini et al. 2019	Retrospective case-control study	534	medical records	-For the first three years postoperatively, suicide attempts and completion accumulatively remained higher among post-STN PD patients [187.20 of 100,000 per year] in comparison to French National Data [23.10/100,000 per year], when adjusted for age, sex and postoperation year. -Recognized history of suicidal ideation/attempts, psychotic symptoms, family history of psychiatric disorders, higher psychotropic medications, baseline poor frontal scores and higher depressive scores (BDI) were risk factors for suicidality.
Seijo Zazo et al. 2018 (159)	Prospective cohort study	30	Beck's Scale for suicide ideation	-No significant change was observed one year after the operation.
Vitek et al. 2020	RCT (three months blinded randomization)	313	CSSRS	-Measured by the C-SSRS, the study found that by the third month of blinded randomization (Active STN-DBS and subtherapeutic STN-DBS), 4/158 attempted suicide, all of whom were in the active group. -Authors had excluded patients with a current or history of suicidality. -No completed suicide was reported one year after the operation.

	Design	No	Tool	Results
Weintraub et al. 2013	RCT (phase I: STN vs. BMT for 6 months. Phase II: STN vs. GPi)	STN n= 255 BMT n=271	UPDRS I – Suicide item PDQ-39 – Proxy symptoms	-No significant difference in suicidal behaviours and proxy symptoms on the Parkinson's Disease Questionnaires 39-item (PDQ-39) after 6 months in both STN and BMT, and *de novo* suicidality was rare (1.9% and 0.9%, respectively). -Proxy symptoms improved better in STN than BMT. -GPi patients reported fewer proxy symptoms, but there was no significant difference regarding *de novo* suicidality between groups after 6 months (STN 1.5% vs GPi 0.7%). -After 2 years of follow-up postoperatively, one case of completed suicide (GPi) and one attempted suicide (STN), both with complicated medical and neurological courses.
Soulas et al. 2008	Retrospective cohort study	200	Medical records	-1% completed suicide, 2% attempted suicide on average of 12 months postoperatively. -No relation was reported between suicidality and change in stimulation settings. -Suicide attempts (3/4) were reported as not serious attempts. -No significant difference was reported between suicidal and non-suicidal in age, disease duration, MDRS and MADRS.
Houeto et al. 2002	Consecutive case series	24	MINI	-Four out of twelve patients with a history of depression had suicide risk on the MINI. -No suicidal attempts were reported after an average of 19 months of postoperative follow-up

RCT: Randomized Clinical Treatment, STN: Subthalamic Nucleus, BMT: Best Medical Treatment, GPi: Globus Pallidum interna, MINI: Mini Neuropsychiatric Interview, MADRS: Montgomery and Asberg Depression Rating Scale, MDRS: The Male Depression Risk Scale, C-SSRS: Columbia Suicide Severity Rating Scale, BPRS: Brief Psychiatric Rating Scale

SUMMARY POINTS: Effect of DBS Parameters on Psychiatric Outcomes

- DBS setting optimization to reduce psychiatric symptoms are possible if motor symptoms are not exacerbated.
- Immediate Psychiatric AEs following stimulation activation can have predictive value for long term psychiatric outcomes.
- The safest DBS contact location in STN regarding psychiatric profile is thought to be the associative region.

2.3.3.7 Effect of DBS Parameters on Psychiatric Outcomes

Eighteen studies (N= 1289), including two RCTs (Okun et al., 2009; Vitek, et al., 2020), one non-RCT (Rossi et al., 2017), seven prospective studies (Abulseoud et al., 2016; Campbell et al., 2012; Dafsari et al., 2018; Ghika et al., 1998; Maier et al., 2016; Mameli et al., 2023; Seijo Zazo et al., 2018), seven retrospective studies (Burdick et al., 2011; Chang et al., 2012; Floden et al., 2018; Kim et al., 2013; Ulla et al., 2011; Welter et al., 2014), one consecutive case series (Perriol et al., 2006), in addition to one experimental study (Petry-Schmelzer et al., 2019) reported the effect of various DBS parameters on psychiatric outcomes. If the optimal motor outcome is not at risk, DBS parameters can be adjusted to minimize psychiatric symptoms. Various emotional and affective experiences have been reported during the optimisation of DBS settings. Patients can have more than one of such experiences, including crying, feeling relaxed, sudden nervousness/apprehension and transient confusion (Abulseoud et al., 2016; Ghika et al., 1998). However, when a psychiatric outcome was believed to be the result of a specific DBS setting, clinicians in a randomized clinical trial (suicidal ideation) (Vitek, et al., 2020) and prospective cohort study (confusion/Pallidal DBS) (Ghika et al., 1998) modified the setting in an attempt to achieve the best outcome. These immediate effects have also offered insight into the nature of the DBS effect on non-motor symptoms. For instance, a prospective study (N= 49) reported that all transient non-motor complications, including psychiatric symptoms, had occurred during left or right monopolar stimulation (Abulseoud et al., 2016). Similarly, left STN- and GPi-DBS stimulation induced significantly lower feelings of exhaustion and improved depressive

score and apathy in an RCT (n=23 GPi, n=22 STN) (Okun et al., 2009) and prospective cohort study (N=42) (Campbell et al., 2012), respectively. Of interest, immediate psychiatric events after activation of the DBS were found to have predictive value for mood and quality of life outcomes up to six months postoperatively (Abulseoud et al., 2016).

As for the long-term effect of DBS settings, although data are scarce, there are some indications that the parameters of the DBS, such as the voltage (Abulseoud et al., 2016; Amami et al., 2017; Chang et al., 2012; Wang et al., 2009), pulse width (Chang et al., 2012), the total electrical energy delivered (TEED) (Mameli et al., 2023), and laterality (Kim et al., 2013; Rossi et al., 2017) may influence psychiatric outcome. Interestingly, the effect of voltage on anxiety was shown to be heterogeneous among participants of a prospective cohort study (N=49), as reducing it changed anxiety to feeling relaxed in some but the opposite in others (Abulseoud et al., 2016). Interestingly, TEED on the right side was reported to be negatively correlated with scores of depressive traits on personality tests[17] (Mameli et al., 2023). The authors of the prospective cohort study (N=20) suggested that with more energy delivered to the right side, more improvement was observed in depressive traits (Mameli et al., 2023). Lastly, among other psychiatric items, apathy showed the least association with stimulation parameters (voltage, frequency, or pulse width) in a case-controlled study (STN n=33 GPi n=15) (Thobois et al., 2010).

One RCT (Okun et al., 2009), three prospective cohort studies (Abulseoud et al., 2016; Campbell et al., 2012) and three retrospective studies (Floden et al., 2018) investigated the effect of electrode location. Contacts located in medial (Abulseoud et al., 2016; Campbell et al., 2012; Floden et al., 2018) and dorsal borders (Liang et al., 2023) of STN on either side are more associated with positive mood in addition to hypomania and euphoria in the same context of a pathologically elevated mood. The authors of a prospective cohort study (N=42) found that, in general, contacts on the right side near medial and dorsal borders of STN induced positive mood (Campbell et al., 2012) as shown in *figure 3*. Another retrospective study also reported an association of improvement in mood symptoms with contacts near the medial borders of left STN (Floden et al., 2018). Medially and anteriorly located electrodes were associated with worsening attentional impulsivity on the Barratt Impulsiveness Scale-11(BIS-II), according to the non-consecutive case series (N=14) (Somma et al., 2022). Of note, in one RCT (n=23 GPi, n=22 STN), activation of ventral contacts in both targets was

[17] The Minnesota Multiphasic Personality Inventory-2 (MMPI-2) was used (Mameli et al., 2023).

significantly associated with self-reported unhappiness, confusion, and low energy (Okun et al., 2009). However, such findings regarding dorsally located contacts conflict with the findings of others. A retrospective study (N=262) found that the effects of STN-DBS on hypomania were significantly associated with deeper contacts in intermediate associative subregion STN (ventral), whereas contacts in zona incerta (dorsal) were infrequently associated with hypomania one year after operation (Welter et al., 2014). In an experimental setting, a cohort of STN-DBS (N=92) was asked to complete the Visual Analogue Mood Scales (VAMS) off-medication in four conditions: optimal DBS setting, activation of dorsal contacts, activation of ventral contacts and DBS off condition. The study reported that 'euphoric' electrode contacts were also more ventrocaudal than 'euthymic' electrodes (Petry-Schmelzer et al., 2019). Furthermore, the same study reported that significant improvement in apathy was associated with electrodes in the ventral border and associative subregion of STN (Petry-Schmelzer et al., 2019). In addition, the increase in apathy severity 6 months after the operation was associated with dorsolateral contacts in a prospective cohort study (N=26)(Boon et al., 2021). However, such outcomes were variably reported among the same cohort. For example, the authors of a prospective cohort study (N=50) found that unspecified non-motor symptoms and quality of life improvement were significantly related to more than one location; medial (Hospital Anxiety and Depression Scale HADS-D, non-Motor Symptoms Scale NMSS), anterior (HADS-D, Non-Motor symptoms questionnaire NMSQ, PDQ-8), and ventral STN stimulation (HADS-A/-D, NMSS, PDQ-8) (Dafsari et al., 2018).

In contrast to these findings, one consecutive case series and two prospective cohort studies failed to find any association between contact locations and the impact of STN-DBS on mood (Perriol et al., 2006; Seijo Zazo et al., 2018) and postoperative satisfaction (N=28) (Maier et al., 2016). Small cohort size and retrospective data collection can partly explain the conflicting results.

[1] -Medial border (bilateral)

- Sudden and transient euphoric sensation and anxiousness (Abulseoud et al., 2016)

- Significant worsening of attentional impulsivity on the BIS-11 for electrodes in the medial and anterior border of STN (Somma et al., 2022)

- Improvement in self-reported mood (Left) (Floden et al., 2018)

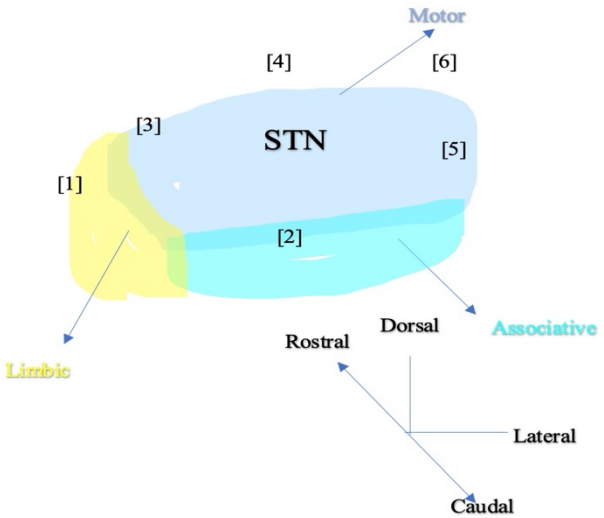
[2] - Ventral and Associative subregion

- Significant improvement of Mood with apathy (Petry-Schmelzer et al., 2019)

- Immediate mood disturbance and confusion (VAMS) was significantly associated with ventrally located contacts (Okun et al., 2009)

-Contacts located near intermediate associative STN were associated with hypomania (Welter et al., 2014)

-Contact located ventrally caused elevation of mood, which lasted several months postoperatively (Seritan et al., 2021)



[3] Dorsomedially located contacts (right): Positive mood (Campbell et al., 2012)

[4] Rostral contacts

-Posteriorly located contacts associated with ADL improvement (Dafsari et al., 2018)

- Reproducible hypomanic state (BRMS) induced by DBS was found to involve mainly contacts that were in substantia nigra (Ulla et al., 2011)

[5] Laterally located contacts; Reduction in LEDD (Dafsari et al., 2018)

[6] The Dorsolaterally located contacts were associated with an increase in apathy severity (Boon et al., 2021)

Figure 10 Summary of Reports on The Relation of Active Contact, Functional Subdivision of STN, And Psychiatric Symptoms

STN = Subthalamic Nucleus, BIS-II Barratt Impulsiveness Scale, VAMS: Visual Analogue Mood Scales, BRMS: Bech-Rafaelsen Mania Scale.

SUMMARY POINTS: Comparing Effects of DBS targets

- Most studies have reported that DBS targets are selected based on motor symptoms.
- STN is the most common DBS Target at 94%.
- There is evidence for a slight difference regarding mood symptoms in favour of GPi.

2.3.3.8 Comparing Targets

Among our results, fifteen studies, including five RCTs (Boel, Odekerken, Schmand, et al., 2016; Follett et al., 2010; Okun et al., 2009, 2014; Weintraub et al., 2013), five prospective cohort studies (Kirsch-Darrow et al., 2011; Okun et al., 2003; Rodriguez-Oroz et al., 2005; Trepanier et al., 2000; Zahodne et al., 2009), three retrospective cohort studies (Pinsker et al., 2016; Volkmann et al., 2001; Westbay et al., 2015)and two consecutive case series (Ardouin et al., 1999; Burdick et al., 2011), reported on comparisons between common DBS targets in PD (N=1385). Results are summarized in *table 7*. Although stimulation targets are usually selected based on the results of individual overall evaluation, these studies attempted to study the differences between targets in terms of psychiatric outcomes. The psychiatric outcomes in general GPi and STN are reported to have equivalent effects in four RCTs (Boel, Odekerken, Schmand, et al., 2016; Okun et al., 2009, 2014; Weintraub et al., 2013) and one consecutive case series study (Ardouin et al., 1999), one retrospective study (Follett et al., 2010) and a prospective study (Kirsch-Darrow et al., 2011) with cohort size ranging from thirteen to eighty-five participants. Among these studies, a study that retrospectively reviewed data from an RCT (Follett et al., 2010) reported that there were no differences in medication use, frequency of psychiatric diagnosis, or cost of inpatient psychiatric care between GPi (n = 85) and STN (n = 76) DBS groups thirty-six months after the operation (Westbay et al., 2015). Furthermore, the DBS effect on mood symptoms was compared between common DBS targets. DBS effect on mood did not differ across targets, according to a retrospective study (Pinsker et al., 2013) and a consecutive case series (Burdick et al., 2011). The consecutive case series with the relatively larger cohort size reported that when the effects of unilateral DBS targeting GPi (n=56), STN (n=195) and ventral intermediate nucleus (Vim)(n=71) were

compared [18], the first two groups scored higher on the anger subscale of VAMS without any significant difference across the two groups (Burdick et al., 2011). Consistently, the authors of a retrospective study reported that depression score was similar across three groups of STN-PD (n=43), GPi-Dystonia (n=10), and ventral intermediate nucleus for dominant tremor PD (n=12) (Pinsker et al., 2013). However, others produced results favouring GPi for mood and emotional well-being in an RCT (Follett et al., 2010) and three prospective studies (Rodriguez-Oroz et al., 2005; Trepanier et al., 2000; Zahodne et al., 2009).

A randomized clinical trial reported that after 6 months, GPi patients (N=152) showed more improvement in BDI score and were significantly more content and less angry (PDQ-39) in comparison to STN patients (N=147) (Follett et al., 2010). When compared to GPi, two prospective cohort studies reported that bilateral STN-DBS led to more immediate (STN n= 49, GPi n=20) (Rodriguez-Oroz et al., 2005) and long-term mood disturbances (STN n=9, GPi n=4) (Trepanier et al., 2000). In contrast, a smaller cohort in a retrospective study showed more reduction in depression scores after STN (n = 11) versus GPi (n = 16) (Volkmann et al., 2001).

Regarding suicidality, the rates of suicidal ideation were equivocal between STN (n=147) and GPi-DBS (n=152) when measured in an RCT (phase II) six months after DBS(Weintraub et al., 2013). Two-year follow-ups of the same population revealed that one patient attempted suicide in the STN group (n=147), and one patient completed suicide in the GPi group (n=152), although the proxy symptoms[19] remained worse in the former group (Weintraub et al., 2013). In addition, a retrospective study (STN n=33, GPi n=15) revealed that there were two suicide attempts in the STN group compared to none in the latter group one year after the operation (Mainardi et al., 2023). As for apathy, a comparison of the unilateral STN (n=33) and GPi (n=15) DBS in a prospective cohort study revealed no difference in the effects of DBS stimulation across the groups of apathy on the AS (Kirsch-Darrow et al., 2011). Finally, regarding confusion, a consecutive case series study suggested that unilateral GPi DBS (n=56) caused significantly more confusion (MMSE) than STN DBS (n=195) (Burdick et al., 2011).

[18] The Vim was selected to treat essential tremor (Burdick et al., 2011).

[19] Selected psychiatric items from the PDQ-39 and SF-36 (Weintraub et al., 2013).

Table 11 Summary of Reports on Comparison of DBS Targets' Effect on Psychiatric Symptoms

	Design	No.	Result
Kirsch-Darrow et al, 2011	Case-control study	Unilateral STN n=33 Unilateral GPi n=15 (control = non-surgical PD n=48)	-No differential effect of DBS on apathy (Apathy Scale) between the two targets.
Weintraub et al, 2013	RCT	Bilateral STN n=147 Bilateral GPi n=152 (control= BMT PD n=134)	-Suicidal ideation was equivocal between two target groups up to six months postoperatively. -Suicidal proxy (the Parkinson's Disease Questionnaire 39 items, Parkinson's Disease Questionnaire-39 and the Short Form 36 items, Short Form-36) symptoms were worse in the Subthalamic Nucleus group after two years postoperatively.
Okun et al, 2014	RCT	Unilateral STN n=16 Unilateral GPi n=14	-Mood (Hamilton anxiety scale, Hamilton Depression Scale, the Young Mania Rating scale) worsened similarly in both groups up to one year after operation. -No between-group differences in psychiatric outcomes.
Okun et al, 2009	RCT	Unilateral STN n=22 Unilateral GPi n=23	-There was no difference between the two groups on the Visual Analogue Mood Scale 7 months after the operation.
Ardouin et al, 1999	Consecutive case series	Bilateral STN n=49 Bilateral GPi n=13	-Depression (BDI) improved in both groups significantly one year after the operation without an inter-group difference.
Boel et al, 2016	RCT	Bilateral STN n=63, Bilateral GPi n=65	-No difference in psychiatric symptoms (Mini-International Neuropsychiatric Interview, Hamilton Depression Scale, Positive and Negative Affect Schedule], Five Factor Personality Inventory-II) across two groups one year after operation. -Globus Pallidum interna DBS led to a reduction of the Young Mania Rating scale scores one year after operation, whereas the Young Mania Rating scale remained stable after one year of Subthalamic Nucleus DBS.

	Design	No.	Result
Westbay et al, 2015	Retrospective cohort study	STN n= 76 GPi n= 85	-No difference was found in medication use, frequency of psychiatric diagnosis, or cost of inpatient psychiatric care between Globus Pallidum interna and Subthalamic Nucleus DBS groups at 36-month follow-up.
Burdick et al, 2011	consecutive case series	unilateral STN n=195 unilateral GPi n=56 Vim n=71	-Subthalamic Nucleus and Globus Pallidum interna groups scored higher on the anger subscale of the Visual Analogue Mood Scale without any significant difference across the two groups. -Unilateral Globus Pallidum interna DBS caused significantly more confusion (Mini-Mental State Examination) than Subthalamic Nucleus DBS.
Rodriguez-Oroz et al, 2005	Prospective cohort study	Bilateral STN n= 49 Bilateral GPi n=20	-Immediate mood side effects were only reported in the Subthalamic Nucleus group.
Trepanier et al, 2000	Prospective cohort study	STN n=9 GPi n=4	-Long-term mood symptoms were more frequent in the Subthalamic Nucleus group.
Zahodne et al, 2009	Prospective cohort study	Unilateral STN n=20 Unilateral GPi n=22	-Despite general improvement in mood and quality of life after unilateral Globus Pallidum interna and Subthalamic Nucleus DBS, emotional well-being (Parkinson's Disease Questionnaire-39) showed greater improvement in patients receiving unilateral Globus Pallidum interna DBS.
Follet et al, 2010	RCT	STN n=147 GPi n=152	-Globus Pallidum interna patients showed more improvement on Beck's depression scale (BDI) score and were significantly happier and less angry (PDQ-39).
Volkmann et al, 2001	Retrospective cohort study	STN n = 11 GPi n = 16	-Reported more reduction in depression scores after the Subthalamic Nucleus.

GPi = Globus Pallidum interna, STN =Subthalamic Nucleus, DBS = Deep Brain Stimulation, PDQ-39: Parkinson's Disease Questionnaire – 39 items, BDI=Beck's Depression Inventory.

2.4 Discussion

The findings of this narrative review included marked heterogeneity within and across the subject area, including the follow-up period, the scope of the investigation and the syndromes covered. This fact limits the discussion and conclusion drawn from results, however, created an opportunity to pinpoint several gaps in the literature. Given that a meta-analysis was not possible to be conducted for subsections due to extreme heterogeneity of designs, cohorts and instruments, the results and discussion were decided to be presented in a narrative manner, based on which a conclusion is drawn subsequently.

The design of the included studies also varied widely, which can partly explain the discrepancy across reports. For example, in retrospective studies, clinical notes were examined, or patients were interviewed retrospectively, whereas in other studies, mental status was evaluated prospectively, which may have yielded more accurate results. Prospective studies with a large cohort and paired PD control with sufficient long-term follow-up are preferable to understand the early and late effects of DBS on psychiatric symptoms. A matched PD group with DBS eligibility as a control group would eliminate DBS ineligibility as a potential source of differences across groups.

To illustrate, the worsening of psychiatric symptoms after DBS over time compared to a matched PD control, whose motor symptoms are managed by medications, could be due to the progression of PD pathology in the former and not necessarily related to the DBS effect. It is challenging to find such a cohort ethically and practically unless patients on the waiting list or those refusing DBS for personal reasons are enrolled. If cost is to be considered, retrospective studies are practical and can still be informative. However, this depends on the data quality recorded and kept at DBS centres. This will be further discussed under the results of the retrospective review in the result and discussion chapter.

There was also considerable variation in the assessment tools used in our results, with a mix of clinician-rated and self-report adopted. Assessment tools used for measuring symptoms, such as BDI and HAM-D for depression (Schrag et al., 2007) or GAD-7 and HAM-A (Leentjens et al., 2008) for anxiety, can produce contradictory results among PD patients. It is possible that these scales assess overlapping symptoms or that they're not suitable for monitoring changes over time. The effect of DBS has also been shown to be more positive on

clinically diagnosed depression than self-rated depression. However, such differences probably reflect the discrepancies between self- and clinician-rated scales. Therefore, assessment tools should include both self-rated and clinician-rated symptom measures, as some symptoms may be better suited for one of them (Cuijpers et al., 2010). In addition, it is crucial to use a unified and suitable set of assessment tools to achieve reproducible and reliable results. This will be discussed in more detail in the chapter on methods and materials. Finally, in the majority of our findings, at baseline neuroleptic use, high subscores on the neuropsychiatric inventory (NPI) and other screening tools were used by the authors as indicators of the presence of psychiatric morbidity (Somma et al., 2022). In prospective cohort studies, such indications would warrant the use of DSM-5 or ICD-11 criteria to define the presence or severity of psychiatric disorders.

That said, most early psychiatric AEs appeared to occur in the first few days following the operation and were mostly transient. These AEs were reported to have improved after adjusting parameters or/and introducing dopaminergic, antipsychotic and antidepressant medications. Of note, the significance of early postoperative psychiatric AEs has not been studied. It is unclear whether they have predictive value for long-term and non-motor outcomes. In addition, even though the current literature makes attempts to identify patients with potential risks of developing postoperative psychiatric symptoms, the majority of such studies have produced contradicting results. Starting with early psychotic AEs, compared to BMT, DBS is reported to produce fewer episodes. However, early psychotic episodes ranging from transient confusion to hallucinations, delusions and aggression are sometimes reported to be as high as 26%, warranting further investigation. Other than having caused prolonged hospitalization and delayed programming of the DBS settings, none reported early psychotic AEs resulting in fatality or removal of the electrodes.

Additionally, not all psychotic episodes are attributed to surgical intervention, but other factors. Some report indicates that psychotic episodes were associated with the withdrawal of apomorphine in individual cases for whom no follow-up was reported (Houeto et al., 2002). A safe strategy for tapering antiparkinsonian medications can prevent the consequences of abrupt DA discontinuation (Koschel et al., 2022). Others relate subacute psychotic events to microlesions caused by implantation (Burdick et al., 2011; Okun et al., 2009). Preventing such consequences could be achieved using surgical techniques that reduce the number of electrodes passes (Somaa et al, 2021). These results support the exclusion of patients with

uncontrolled psychotic symptoms from DBS surgery while showing DBS to be generally safe in terms of postoperative psychotic AEs.

Regarding postoperative mood changes, depression, anxiety, hypomania, and emotional instability are all reported and investigated to identify their risk factors. Depression following the operation is reported to be the most common mood symptom, followed by anxiety and hypomania, emotional instability, and euphoria. Except in a few small studies, most mood changes were reported to be transient and responsive to activation of DBS or pharmacological treatment. In contrast, apathy, a complex neurobehavioral disorder, is less commonly reported but tends to persist, which supports theories of a distinct neural network dysfunction (De Waele et al., 2022). Furthermore, the effect of DBS in ameliorating ICDs has been reported by several studies with different designs and cohort sizes and is primarily due to a decrease in dopaminergic medication after the operation. It appears that this effect is not consistent across all ICDs. Our review found that problematic gambling was the most responding ICD, but another review found that compulsive shopping was more responsive and binge eating was the least responsive one (Kasemsuk et al., 2017). After DBS, there have been reports of *de novo* ICDs, which are believed to be a result of persistent high postoperative dopaminergic dosage, undisclosed preoperative impulsive behaviours, and poor motor improvement (Lim et al., 2009). Others who did not find a relationship between improved or persistent ICDs and postoperative dopaminergic reduction also reported minimal LEDD reduction nine months following the operation. This study included cases of unilateral STN-and GPi-DBS among a small cohort, which may explain the lack of reduction of postoperative dopaminergic medication compared to bilateral STN-DBS, as the latter is associated with a greater reduction in LEDD following the operation (Goelz et al., 2017).

Furthermore, several risk factors are identified for the persistence and worsening of ICDs after the operation, such as personality traits, lack of LEDD reduction, contact location, gender, and age. Age seems to increase the risk of *de novo* and worsening ICDs differently. Younger age is associated with *de novo*, while older age is associated with worsening ICDs. Gender also increases the risk of individual ICDs.

Suicidal ideation and suicide attempts were not associated with motor improvement but with a history of suicidality, suggesting a need for thorough pre- and postoperative evaluation involving both patients and relatives in the process (Porat et al., 2009). Furthermore, the comparison of early psychiatric AEs after DBS to those of alternative treatment was mainly in favour of DBS therapy, although results collectively support a need to closely monitor

patients with active psychotic symptoms after DBS operation. In terms of other risk factors for early postoperative psychiatric symptoms, age, cognitive function, and psychiatric history are associated with mood changes, psychotic events, and suicidality.

As for long-term postoperative effects, psychotic symptoms initially worsened and then stabilized over time. However, in longer follow-ups, i.e., beyond 5 years, others reported either improvement or no change. Initial worsening of psychosis-related items on assessment tools is often reported but does not commonly meet the criteria for clinical significance. As for preoperative psychotic symptoms, unless they are controlled, patients with active psychotic conditions are considered ineligible for DBS treatment (Sarno et al., 2019). Reports of DBS effects on mood symptoms vary in the first 12 months following the operation. The majority of these reports point to either no change or worsening of depression and anxiety in the first year following GPi and STN DBS. Worsening was particularly shown to be significant for anxiety and cognitive-emotional symptoms of depression when compared to matched PD patients. This worsening might have prognostic value for cognitive dysfunction, a common devastating non-motor feature of PD. Anxiety has been reported in previous studies to be associated with cognitive impairment, memory function in particular (Dissanayaka et al., 2017). However, mood symptoms improve when patients are followed up for 1 to 11 years. Although the mood-related symptoms can return to baseline in some cases, this is unlikely to happen beyond 5 years postoperatively. As a recommendation for clinicians, mood should be monitored, and long-term psychological therapies should be offered when necessary to enhance coping skills for both patients and carers. This may reduce the mood-related burden on patients and carers (Gülke & Pötter-nerger, 2022; Westerink et al., 2023).

As for the prediction of post-DBS mood outcomes, gender, sleep, quality of life, history of depression, higher self-rated preoperative tremor and performance on frontal lobe function tasks were found to be potential predictors for postoperative depression worsening or *de novo* depression. One interesting finding was that there was greater improvement in clinically diagnosed mood disorders compared to self-reported symptoms after DBS therapy. This finding indicates the importance of using structured or semi-structured interviews when assessing mood, as self-rated symptoms may be influenced by expectations, personality traits, etc. (Cloninger & Zohar, 2011). Gender is another factor of interest which has been identified as a risk factor for several post-DBS psychiatric outcomes. However, in a retrospective review of a large cohort in the USA, females were underrepresented (Deuel et al., 2023).

According to the authors, female patients were referred to DBS clinics less frequently than men (Moisan et al., 2016). They argue that although the reasons are unknown, it could be the patient's personal preference or providers' bias. This may contribute to the underrepresentation of female participants in such studies as most of them are recruited their participants in clinics.

Regarding apathy, the majority of studies reported that this worsens up to 24 months after DBS operation. However, it was not significant in all studies and responded to either antidepressants, dopamine, or both. When the DBS effect on apathy scores was compared to other advanced treatment options, including the combination of unilateral STN-DBS and contralateral subthalamotomy, only apomorphine therapy showed any advantage. Potential predictor factors for apathy outcomes after DBS have been reported in different studies. The identified preoperative risk factors, including hyperdopaminergic profile and higher depressive and UPDRS, part three, motor scores, require further investigation to understand the underlying association. Postoperative predictors identified included dopaminergic medication reduction, advanced age and cognitive impairment. These findings must be replicated to confirm the relation of apathy with various subscores of the utilized scales. For example, the decline in verbal fluency did not correlate with postoperative apathy, whereas executive dysfunction did (Denheyer et al., 2009).

Moreover, both mood and behavioural symptoms following DBS therapy might have strong associations with performance on various cognitive domains before operation. This suggests that preoperative cognitive function could be used as a guide for customizing postoperative monitoring. Finally, suicidality is also reported to be higher in long-term among the DBS group in comparison to age-matched non-clinical populations; however, not significantly higher than patients on BMT. This may be due to the burden of living with advanced PD or frustration because of no improvement in motor symptoms. However, in terms of risk factors, being single and having a history of impulsivity, depression, and suicide attempts have been identified. Clinical interviewing and carer involvement can assist in reducing instances of patients concealing relevant stigmatized psychiatric symptoms such as impulsivity and suicidality (Kennis et al., 2023).

Studies of the effect of DBS parameters on psychiatric outcomes have produced insightful information. According to these studies, immediate psychiatric events, such as crying, feeling relaxed or apprehension following DBS activation, may respond to parameter adjustment. Some studies also report that these symptoms can predict mood and quality of life outcomes.

However, most parameters are not extensively studied. For example, while polarity has been identified as a risk factor in inducing psychiatric symptoms, such findings have not been replicated. In addition, reports on the effects of DBS setting vary between studies. A common finding is that higher voltage, sometimes required to optimise motor symptoms in a majority of patients, can increase depression and anxiety scores. However, due to the small number of participants and low-quality design, a conclusion cannot be drawn from most of these studies. Therefore, larger cohorts have to be recruited to understand if patients who require higher voltage DBS settings to achieve an ideal motor state are at greater risk of developing psychiatric symptoms. These consequences also require more sophisticated programming approaches considering non-motor symptoms, including psychiatric symptoms (Wagle Shukla et al., 2017). Other neuroimaging studies emphasise the importance of targeting selective brain connectomics and neural rhythms for optimal motor outcomes and reduced non-motor effects (Hollunder et al., 2023). Studies of DBS parameters have also investigated the relationship between electrode locations and psychiatric symptoms. Although their results are also heterogeneous, they have produced some valuable information. However, such objectives require more complex neuroimaging-based studies since the anatomy of DBS targets is complicated.

Contacts in the lateral part of STN lead to greater LEDD reduction; if replicated, this approach would benefit patients suffering from DA side effects. Furthermore, contacts located in the ventral STN (associative subregion) were linked to improved depression and apathy but also to induced confusion and hypomania. Lastly, in the limbic subregion, bilateral stimulation induced sudden and transient euphoric sensations; however, unilateral stimulation on the left side improved self-reported mood symptoms. We also reviewed studies where DBS targets were compared regarding psychiatric outcomes. Although choosing the ideal target between STN and GPi mainly depends on motor and cognitive function, their effects on psychiatric symptoms are different, with most studies reporting a slight superiority of GPi for psychiatric outcomes. That said, GPi DBS has also been reported to significantly induce more confusion when compared to STN DBS. However, the quality of studies is generally insufficient to draw definitive conclusions.

2.5 Conclusion

The period from operation is found to make a difference when reporting the DBS effect on psychotic AEs. Reports indicate that immediate postoperative psychotic AEs are common and mostly reversible, regardless of the design and size of the cohort of the included studies. In long-term postoperation follow-ups, however, preoperative psychotic symptoms were reported to worsen in prospective cohort studies. Despite these findings, it has also consistently been reported that DBS patients have a lower rate of reported incidents of psychotic symptoms in long-term follow-ups than medically treated patients. Conversely, the study's design made a difference in reporting the prevalence of immediate postoperative mood disturbances and long-term mood outcomes. This is mainly due to the difference in rating agents, i.e., whether it is a patient, clinician, or an informant. It can also be due to differences in measuring instruments with varying specificity and sensitivities. Therefore, individual psychiatric symptoms need to be observed in high-quality studies to fully understand their nature and prognosis.

Current literature on the effect of DBS on apathy also relies on small cohorts with a lack of proper control groups. It has been demonstrated that apathy tends to remain stable or worsen after the DBS operation. Conversely, in several studies, impulsive behaviours are shown to reduce after the DBS operation. However, this decline is neither stable nor the same for all impulsive behaviour subtypes. For example, gambling behaviours are reported to have a better response to DBS. Also, certain personality traits, such as obsessive-compulsive traits, are more likely than others to be affected by DBS, but this finding needs to be replicated in high-quality studies. If personality traits are studied properly, they may have predictive value for PD-DBS postoperative psychiatric outcomes. As for immediate and long-term postoperative suicide ideation, attempt, and completion, these are all reportedly more common among the PD-DBS group than the same age group in the normal population but not higher than matched PD groups receiving other modes of treatment.

Studies of DBS laterality, parameters and location of contacts have produced relevant findings that can inform future studies. According to our results, despite the results not being replicated sufficiently, contacts located near the medial and dorsal border may produce fewer mood symptoms. Future studies should consider more sophisticated methodologies, such as live records of local field potential, as there is heterogeneity in the effect of contact location

in the same cohort. The association between apathy and a contact location is distinct and requires further investigation in larger cohorts. Finally, when the two common DBS targets, GPi and STN, were compared, findings indicated that they did not have a major distinctive effect on psychiatric outcomes in multiple studies.

In conclusion, an extensive review was carried out on a broad topic through this narrative review. This review identifies areas not studied enough to conclude from. In the current review, it is concluded that multiple studies have provided valuable but limited information on how DBS affects the psychiatric aspects of Parkinson's disease. That said, the heterogeneity of their results also demands higher quality studies emphasising psychiatric outcomes. Limitations of the majority of our results include but are not limited to, small cohorts, varied assessment tools, and different study designs. Multicentre studies that create a unified data set would address many of these issues. Advanced neuroimaging and other advanced investigations could result in more valuable and informative results.

2.6 The Summary Points (Clinical Notes)

1. **Early Postoperative Psychotic AEs**

- Psychotic symptoms are not uncommon after DBS (5-25%).
- The onset may coincide with surgery or apomorphine withdrawal.
- The onset ranges from intraoperative period to weeks after.
- Antipsychotics are reportedly helpful.

2. **Early Postoperative Mood and Apathy AEs**

- Mood alterations and apathy symptoms are common after DBS (10-45%).
- Such mood AEs range from feeling sad to a hypomanic episode, and are mostly transient.
- Apathy symptoms tend to be more persistent

3. **Risk Factors for Early Psychiatric AEs**

- Age, cognitive function and history are patient related risk factors.
- Older age is associated with confusion postoperatively.
- Fewer number of electrodes passes may reduce the risk.

4. **Long-term Effects on Psychotic Symptoms**

- Psychotic symptoms tend to return to baseline.
- Psychotic symptoms are less common after DBS than medical treatments

5. **Long-term Effects on Mood Symptoms < 12 Months**

- Depression symptoms mainly range from stable to improvement.
- On/off stimulation status has little immediate effect on Mood.
- Anxiety tends to reduce postoperatively.
- Improvement in mood can be related to the improved QoL

6. **Long-term Effects on Mood Symptoms > 12 Months**

- Mood symptoms tend to improve compared to baseline.
- Off/On-period dysphoric/euphoric mood and anxiety reduced.
- Beyond 5 years after surgery, mood remains mostly stable.
- Improvement in mood is relatable to the improved QoL.

7. **Predictive Factors for Mood Outcomes > 12 Months**

- Pre-DBS QoL, tremor severity, sleep quality, psychiatric history and frontal lobe function are potential predictive factors.
- Higher academic degree can potentially predict less improvement.

8. **Post-DBS Mood Outcome Compared to Alternative Treatment**

- Early outcomes are in favour of medical treatment, but not the long-term follow-ups
- Post-DBS irritability is more common than in medical treatment.

9. **Apathy Long-term outcomes > 12 Months**

- Apathy reportedly worsens or remain unchanged.
- On non-apathy specific scales, related items showed improvement.

10. **Post-DBS Apathy Outcome Compared to Alternative Treatment**

- The comparison to other modes of treatment, including medical treatment, apomorphine, revealed no difference in short-term.
- In the long-term, Apathy is more common after STN-DBS.

11. Long-term Effects on ICBs > 12 Months

- Long-term effects are reportedly promising.
- Individual ICBs respond differently.
- The prevalence of *De novo* cases are not uncommon at 8-15%.

12. Predictive Factors for ICBs Outcome > 12 Months

- Individual ICBs can have distinct predictive factors.
- Personality traits, reduction in DRT, younger age predicted improvement.
- Gender and psychiatric outcomes are predictive of impulsivity in general.
- De novo cases of ICBs are common.
- There are conflicting results about relation between personality traits and impulsivity post-DBS.
- There are conflicting results about relation between DA use and impulsivity post-DBS.

13. STN-DBS Effect on Personality Traits

- Variably Notable changes have been observed in personality traits, by informant and patients.
- Personality traits including extravagance, harm avoidance, persistence are reportedly improved following DBS.
- The variability of tools which were used to measure traits is the main issue in the reviewed studies.

14. DBS Effect on Suicidality

- Suicidality include suicidal ideations to completion.
- Suicidality has been reported at 0.45% to 31%.
- Suicide completion is rare, but slight above the general population.
- Being single, having a history of obsessive-compulsive disorder, previous suicide attempt and impulsivity are suggested to be the risk factor.

15. Effect of DBS Parameters on Psychiatric Outcomes

- DBS setting optimization to reduce psychiatric symptoms are possible if motor symptoms are not exacerbated.
- Immediate Psychiatric AEs following stimulation activation can have predictive value for long term psychiatric outcomes.

- The safest DBS contact location in STN regarding psychiatric profile is thought to be the associative region.

16. Comparing Effects of DBS targets on Psychiatric Outcomes

- Most studies have reported that DBS targets are selected based on motor symptoms.
- STN is the most common DBS Target at 94%.
- There is evidence for a slight difference regarding mood symptoms in favour of GPi.

2.7 Limitations:

2.7.1 Limitations in Reviewed Studies:

1- There are several papers with small cohorts with no control group.
2- The reporting of many studies is of low quality, with insufficient detail of samples, low-quality explanations, and failure to report statistical details such as effect sizes.
3- However, several studies have good quality presentations of all relevant details.
4- There is a large diversity in measuring tools with very different psychometric and normative properties for the same body of symptoms.
5- There are also a lot of terminology differences across many studies.
6- In many papers, the psychiatric symptoms were reported with no information about baseline data or further information on the nature of symptoms.

2.7.2 Limitations in the Scope and Conduct of the Review

Our search scope was written to be ambitiously broad to review all symptoms evaluated in the CRISP study. This produced a very large number of heterogeneous studies in terms of cohort size and methodology. As a result, identifying the contributing factors and diving deep into the contradictions became complicated. The conclusion drawn from above results is based on the fact that this is a narrative review. A more rigorous conclusion can only be drawn when a meta-analysis with a more specific scope is conducted. Nevertheless, in the current narrative review, several themes were identified to facilitate the interpretation. Furthermore, the individual symptoms and symptoms covered by the CRISP study will be further reviewed and discussed in the *chapter 5*.

2.8 Future Works

The scope of review of DBS effects on psychiatric symptoms after the operation should be limited to individual symptom(s). At this point, a meta-analysis would provide more conclusive results than a narrative review, which is crucial for identifying relevant studies and describing their outcomes. A meta-analysis will also allow to analyse the results of measuring instruments that measure a specific aspect of a given psychiatric symptom, such as the cognitive aspect of depression or the social aspect of apathy.

Chapter 3: Clinical Response of Impulsivity After Brain Stimulation in Parkinson's Disease (CRISP Study)

3.1 Background

In January 2014, the UK DBS Network was formed from the Parkinson's Disease Clinical Studies Group (then under the National Institute for Health Research NIHR) to share best practices, collect information, and facilitate research across all DBS centres in the UK. Members of the group are all consultant neurologists, neurosurgeons, neuropsychiatrists, specialist nurses and academics from 17 DBS implanting centres. The Parkinson's Excellence Network supports the network. It meets every six months or yearly. The first initiative was to create a database of essential clinical data, including age, sex, United Parkinson's Disease Rating Scale (UPDRS), information on surgery, targets, device information, QoL and complications on up to 300 DBS cases a year across the UK. DBS surgery is routinely funded as part of standard care by the National Health System (NHS), England (Clinical Commissioning Policy: Deep Brain Stimulation (DBS) In Movement Disorders Prepared by the NHS Commissioning Board Clinical Reference Group for Adult Neurosurgery, 2013). During the first 6 months of the registry, 84 entries were made (up to January 2017). The UK DBS Network has identified the need and the opportunity to add a specific research component to this database, the cost of which is not covered by NHS England. If every UK DBS centre in the network contributes, it can recruit many consecutive patients who have undergone DBS, creating a large and valuable DBS research resource that presents deliverable DBS research opportunities for the UK. The first proposed study addresses the relationship of ICBs with DBS-STN.

The study was designed to recruit many participants (target n=100) from multiple UK DBS centres. The study's objectives were to address unanswered questions about the effects of deep brain stimulation (DBS). Another concurrent objective was to create and implement an online shared research database between participating DBS centres. It was believed that implementing a secure and accessible online platform would enable seamless and time-efficient collaboration between UK DBS centres through the shared database. Therefore, the vision was to connect all UK DBS centres and create a large data pool for future relevant research projects. The National

Health Service (NHS) already provides online databases for individual DBS centres. However, studies like the CRISP study showcase the utility of including a shared platform. Specific measures were taken in the CRISP study to make this vision feasible and minimise the burden of implementing the shared platform on local staff, participants, and research coordinators. It was also part of my mission to work with Orion MedTech to create the prototype database that completes the vision. Even though the prototype platform is finished, the data collection team did not use it as planned before the outbreak due to its delayed completion. The CRISP study's methodology and materials are detailed in the following subsections. The data analysis strategy is also outlined here.

3.1.1. DBS-STN and ICBs Relationship

Over a decade ago, it was recognised that the interaction of ICBs and DBS would be complex when members of our group asked, "Is pathological gambling an indication or a contra-indication for DBS?"(Samuel & Voon, 2005). Since then, studies attempting to address this question have produced inconsistent results, and so we now wish to use the extensive data pool of UK DBS patients and our national collaboration to address this important and common question, as it is faced in DBS clinics regularly (Pondal et al., 2013).

DBS is only indicated for movement symptoms in PD. Therefore, by using DBS to control Parkinsonian motor symptoms, it is hypothesised that the drug-induced side effects associated with dopaminergic medication could be reduced because postoperative drug reduction is usually the norm after STN DBS. There is an evolving hypothesis which suggests that if medication (in particular dopamine agonists) is reduced following DBS, then ICBs may improve. However, there is concern that apathy and other symptoms of dopamine agonist withdrawal syndrome (DAWS) might then develop postoperatively (Lhommee et al., 2017; Okun & Weintraub, 2013; Volkmann et al., 2010). On the one hand, there has been interest in the potential use of DBS to aid in treating PD patients with established ICBs, mainly targeting the STN (Bandini et al., 2007; Knobel et al., 2008; Lhommée et al., 2012; Shotbolt et al., 2012). A great deal of scientific evidence suggests that the subthalamic nucleus is important in delaying motor responses and reducing impulsive behaviour (Frank et al., 2007; Jahanshahi et al., 2015). Not all ICBs respond to DBS similarly; for example, pathological gambling is reported to have a better response to DBS than other reported ICBs (Kim et al., 2013).

On the other hand, STN DBS might worsen impulsivity through a direct effect on STN function induced by electrical stimulation of the intended target or surrounding structures. Overall, it is likely that multiple different factors may potentially be important in predicting changes in ICBs following surgery, including predisposing factors (sex, age and symptoms of ICBs preceding surgery), operative factors (target), and postoperative factors (medication changes, stimulator settings). Published studies into the effect of DBS on ICBs have been case reports and case series. Furthermore, these published studies have focused on the presence (yes/no) of ICBs, with little information on the severity assessment (changes in frequency/intensity/impact). The results from the studies have been very mixed, with some studies demonstrating worsening ICB after DBS and others demonstrating the opposite (Amami et al., 2015; M. Broen et al., 2011; Lim et al., 1148; Volkmann et al., 2010). In summary, the current data are conflicting.

3.1.2. Treatment of ICBs

There is a paucity of evidence-based data to guide the management of ICBs in PD (Rabinak & Nirenberg, 2010). Current practice is to reduce or withdraw dopamine agonist medication, which will usually lead to an improvement or resolution of ICBs (Samuel et al., 2015). However, a proportion of symptoms can persist, and some patients cannot tolerate medication reduction. Medication withdrawal is associated with two potential complications: firstly, some patients are likely to develop worsening motor symptoms (as the motor state is now less treated); secondly, some patients may develop dopamine agonist withdrawal syndrome (DAWS), which is a neuropsychiatric syndrome akin to substance misuse withdrawal, characterised by symptoms including anxiety, apathy, depression, and diaphoresis (Pondal et al., 2013; Thobois et al., 2010). Like other psychostimulant withdrawal syndromes, DAWS is consistent with the lack of response to levodopa, antidepressants and anxiolytics and the improvement with DA replacement. Atypical antipsychotic medications are sometimes added to a patient's drugs to improve ICBs, but there is very little evidence base to guide this treatment (Papay et al., 2011; Rabinak & Nirenberg, 2010). Only one randomized trial of cognitive behavioural therapy (CBT) from our group was shown to help some aspects in individual cases (Okai et al., 2013; Samuel et al., 2015). One strategy would be to proceed to STN-DBS, which should lead to a reduced requirement for DAs and, therefore, a reduction in ICBs, based on the reports discussed in the previous section. In the CRISP study, this hypothesis will be investigated.

3.1.3. ICBs Scales

The lack of unified criteria has affected the study of risk factors and prognosis of ICBs in PD (Evans et al, 2019). However, there are several validated rating scales available to measure ICBs. These scales can be divided into those that are used as screening tools and allow a dichotomous outcome (Yes, No) or categorical outcomes, which assess the presence or absence of ICBs, and those which grade the severity of ICBs. Screening scales include DSM-IV screening, the Questionnaire for Impulsive Compulsive Disorders in PD (QUIP) and the Minnesota Impulsive Disorders Interview (MIDI) (Christenson et al., 1994; Evans et al, 2019; Weintraub et al., 2009, 2015). The Ardouin scale is a semi-structured interview that documents what are termed "hypodopaminergic" behaviours, including apathy and depression, as well as "hyperdopaminergic" behaviours, including ICBs (Ardouin et al., 2009). Ardouin scale completion takes up to two hours, making it less practical time-wise in studies such as the CRISP study in which multiple scales will be used (Rieu et al., 2015). Other more practical quantitative scales allow us to follow up ICBs over time and measure small changes in ICBs rather than simply document the presence or absence of severe ICBs. Quantitative measures include: -The Questionnaire for Impulse Control Disorder in Parkinson's Disease – Rating Scale (QUIP-RS) and the PICS, which will be discussed in more detail in the material section in *Chapter 3*. Both questionnaires will screen for 4 ICDs: compulsive gambling, hypersexuality, binge eating, and compulsive shopping, in addition to the three related ICBs, hobbyism, punding and DDS.

A larger number of patients can be detected with mild ICBs efficiently, and the presence of ICBs can be quantified using a low threshold on the QUIP-RS. Therefore, participants scoring above one for any ICBs on QUIP-RS will also be assessed with Research Fellow (RF) rated PICS, which can assess ICBs in more detail. This two-stage approach will enable us to capture as many patients with ICBs as possible in the study and, importantly, target resources most efficiently towards those with the most significant symptoms. Those who do not score positive on the QUIP at baseline will fill out the scale in the subsequent follow-up and other neuropsychological scales to detect any change or development of ICBs.

Using quantitative scales will, therefore, enable a more detailed study of ICBs and other potential neuropsychological aspects. When published, the results of this study will guide clinicians when counselling PD patients with and without impulsivity prior to DBS. It will,

therefore, directly influence clinical care nationally. Furthermore, members of our study team have extensive expertise in ICBs and DBS, with 7 peer-reviewed publications directly related to ICBs and many more related to DBS and PD in general, and so are in an excellent position to deliver results from this study and subsequently disseminate its findings to the Parkinson's community.

3.1.4. Utilizing Results from Other Assessed Psychiatric Symptoms in The CRISP Study

Similar to impulsivity, reports on the effect of DBS-STN on other psychiatric symptoms are conflicting (Pusswald et al., 2019; Schadt et al., 2006; Strutt et al., 2012). As discussed in previous sections, psychiatric symptoms such as depression, anxiety, psychosis, apathy, and cognitive impairments are very common among PD patients. Furthermore, as noted in *Table 2*, unless the psychiatric disorder is unstable and evident, they are not a common reason for the exclusion of DBS therapy (Defer et al., 1999). Therefore, this thesis will analyse the results of the other assessments conducted for psychiatric symptoms, quality of life, personality traits and carer's burden to investigate their response to STN-DBS. The next chapter reviews the latest literature on the impact of DBS on these variables.

3.2 Objectives

3.2.1 Primary Objectives

I. Frequency of ICBs in STN-DBS candidates before operation
II. Relationship of ICBs frequency at baseline with demographics, medication and psychiatric symptoms
III. Effect of STN-DBS on ICBs
IV. Prevalence of *de novo* ICBs following DBS-STN
V. Relationship of ICBs changes and demographics, medication and psychiatric outcomes

3.2.2 Secondary Objectives

I. Frequency and relationships of psychiatric symptoms in STN-DBS candidates before operation

II. Effect of DBS-STN on other measured psychiatric symptoms and personality traits
III. Effect of DBS-STN on quality of life
IV. Effects of DBS-STN on Carers burden

3.3 Methodology and Materials

The **C**linical **R**esponse of **I**mpulsive behaviours to deep brain **S**timulation in **P**arkinson's disease (CRISP) study is the focus of the current thesis. This chapter presents the design and methodology for the CRISP study and, subsequently.

3.3.1 Methodology

The prospective study is designed to assess the effects of Globus Pallidus interna (GPi)- and Subthalamic Nucleus (STN)- Deep Brain Stimulation (DBS) therapy on impulsive behaviours and other psychiatric symptoms in patients with Parkinson's disease (PD). In this thesis, only STN-DBS cases are included, as the number of participants recruited into the study for the former target was small (n=4).

3.3.1.1 Study Setting

Of the total seventeen DBS centres in the UK, seven centres agreed to recruit PD consecutive patients eligible for DBS therapy, *Table* 12. Their clinicians selected all potential participants for DBS therapy to treat their motor symptoms per routine clinical care. As per standard care, a multidisciplinary team at each centre assessed all patients pre-DBS to confirm their eligibility for STN-DBS. For the CRISP Study, potential participants were approached by a clinical care team member, the research link to this study, i.e., the local investigators (LIs). The names of contributors and involved institutes are displayed in *Table* 12. Potential participants received a verbal invitation from local investigators to consider joining the study along with their carers. Participants who agreed to consider joining the study were provided with more information through an introductory package sent to them by mail/email or in person at the clinic. The introductory pack contained:

1. Introductory Instruction sheet
2. Study Information sheet (one for patient, one for carer)
3. Two Consent forms (one for a patient and one for a carer)

4. Self-rated questionnaires (T0) to be completed by patients and carers before stimulation activation (see *Figure* 11).
5. Prepaid Royal Mail return envelope.

The protocol for this study was written according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and was published on Clinicaltrials.org (NCT04811807) (See *Appendix 4*). The South London and Maudsley NHS Foundation Trust (SLaM) sponsored the study; D.O. was the chief investigator (See *Appendix 14*). I conducted the study as a research fellow (RF). I was enrolled in a self-funded PhD programme at King's College London – Institute of Psychiatry, Psychology and Neuroscience (IOPPN), Department of Old Age Psychiatry. I was granted an honorary contract from SLAM to serve as an RFF in this study. My first to third academic supervisors were as follows: Dr Paul Shotbolt, clinical senior lecturer and consultant neuropsychiatrist; Dr David Okai, consultant neuropsychiatrist at SLaM; and Professor Michael Samuel, neurologist at King's College Hospital.

Table 12 Participating Centres in CRISP Study

Contributors	**Institutes**	
Chief Investigator	**The study sponsor**	**City**
Dr David Okai, Neuropsychiatrist	South London and Maudsley NHS Foundation Trust	
Research Fellow	**Academic sponsor**	*London*
Arteen Ahmed, Psychiatrist	King's College London – Institute of Psychology, Psychiatry and Neuroscience	*London*
Local investigator (LI)	**Participating DBS Centre**	
Dr Paul Shotbolt - Neuropsychiatrist	King's College Hospital	*London*
Prof Monty Silverdale - Neurologist	Salford Royal NHS	*Salford*
Dr Edward Newman – Neurologist	NHS Greater Glasgow & Clyde	*Glasgow*

Dr Antonella Macerollo – Neurologist	The Walton Centre NHS Foundation Trust	*Liverpool*
Prof Nicola Pavese – Neurologist	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	*New Castle*
Dr Nagaraja Sarangmat – Neurologist	Oxford University Hospitals NHS Foundation Trust	*Oxford*
Dr Anjum Misbahuddin - Neurologist	Barking, Havering and Redbridge University Hospitals NHS Trust	*Romford*

3.3.1.2 Study Time Points and Timeline

Once potential participants had agreed to consider joining the study, an introductory package was sent to them, including patient and carer information sheets and consent forms. This stage was to invite them to join the study formally. After agreeing to participate in the study, they signed consent forms (See *Appendix 5 and 6)*, completed the enclosed self-rated scales (T0), and returned them to us at the Maudsley Hospital. The study only required a limited number of questionnaires for participants during clinical follow-up, minimise the burden on patients and the health team. The demographic and medication-related information were collected from participants or LIs. *Figure* 11 shows the timeline and time points of the follow-ups. *Table* 12 displays more information on collectable data. There were four time points for data collection, including the baseline and three follow-ups. The time window to complete the baseline data collection starts six weeks before the DBS operation and ends when the DBS device is activated[20]. The completion window for data gathering at other time points is four weeks. The 1st follow-up was three months after the operation date. The 2nd and 3rd follow-ups were 6 and 12 months after the operation. This thesis uses the data collected to date (September 2023) for baseline (T0) and the 6-month post-operative follow-up (T2). At each time point, three sets of data were collected: 1) self-rated questionnaires that were sent to participants (See *Appendix 7 and 8*), 2) RF-rated questionnaires completed over the phone (See *Appendix 9*), 3) The relevant data from medical records, including demographics (age, gender, PD duration, ethnicity,

[20] The DBS device is typically activated 4-6 weeks after the operation, depending on general well-being of patients and schedules of DBS clinics.

employment status[21]), DBS parameters (Lead location, laterality, activation date, frequency, voltage, wave width), and PD and other PD-related medications. The latter was collected either from patients or LIs.

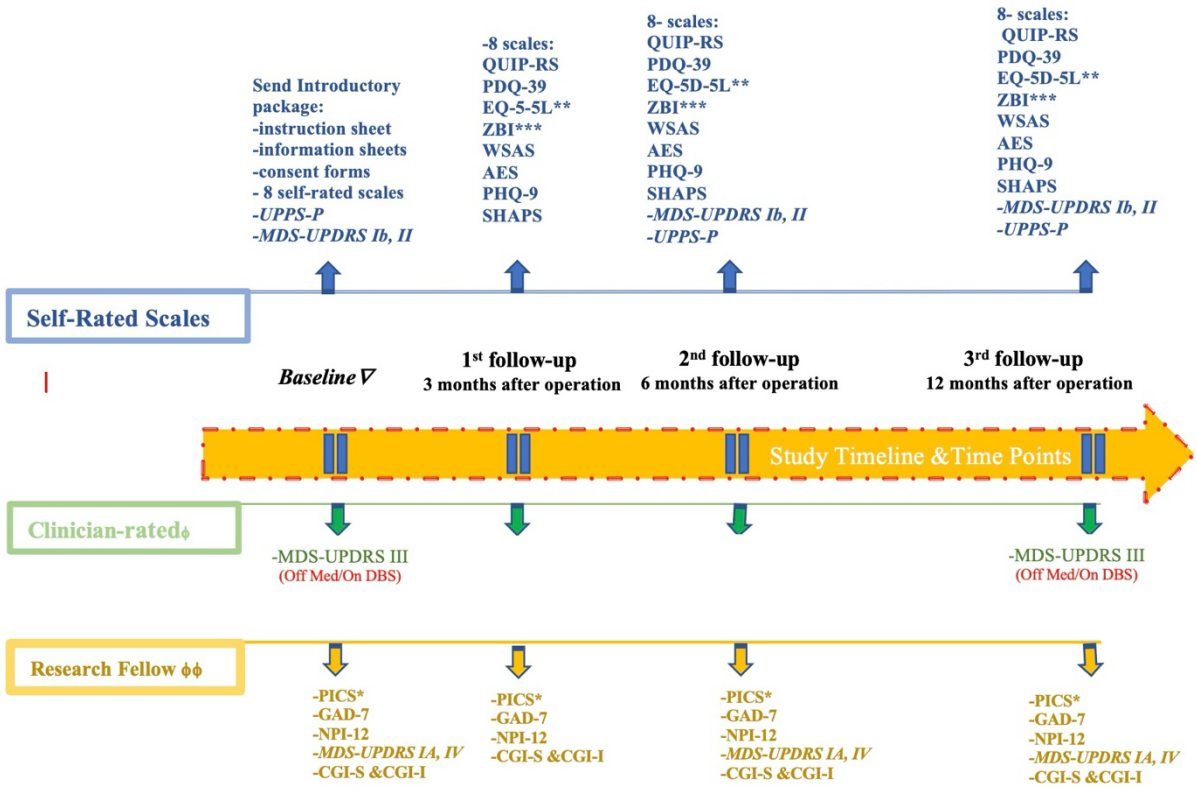


Figure 11 Timeline of Research Follow-ups

***UPPS-P**= Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behaviour Scale, **MDS-UPDRS**= Movement Disorders Society Unified Parkinson's disease Rating Scale, **QUIP-RS**= Questionnaire for **Impulsive**-Compulsive Disorder in Parkinson's disease Rating Scale, **PDQ-39**= Parkinson's Disease Questionnaires-39 items, **EQ-5D-5L**= European Quality of life-5Dimensions-5Levels, **ZBI**=Zarit Burden Interview, **WSAS**= Work and Social Adjustment Scale, **AES**=Apathy Evaluation Scale, **PHQ-9**= Patient Health Questionnaire-9 items, **SHAPS**=Snaith-Hamilton Pleasure Scale, **PICS**= Parkinson's Impulse Control Scale, **GAD-7**= General Anxiety Disorder-7 items, **CGI-S**= Clinical Global Impression-Severity, **CGI-I**= Clinical Global Impression- Improvement, **NPI-12**=Neuropsychiatry Inventory-12 items.*

**PICS is done only for those who score above 1 on QUIP-RS*

***EQ-5D-5L is completed by both carer and patient, measuring their quality of life separately*

**** This is completed by the carer only*

ϕ to be done by local investigators in the clinic

ϕϕ to be done by RF over the phone

∇ completed within 6 weeks before operation until activation of the DBS.

[21] Employment status is collected from the work and social adjustment scale (WSAS) which is completed by participants at baseline and other follow-ups.

Scales that are written in italics are not completed at 1st follow-up. CGI-S and CGI-I are not utilised in the data analysis for the current thesis.

In this thesis, only demographics and medications were included from the medical records that were planned to be collected. Of all questionnaires, the Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part I, II, III, IV and the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behaviour Scale (UPPS-P) were the only two scales that were not collected at the 1st follow-up, to reduce the burden on participants, RF and LIs. Likewise, the usual routine was followed for the UPDRS part III, completed by the local clinical care team: once at the baseline and once at the 3rd follow-up (on and off medication). In this thesis, the UPDRS III was not included. This part was planned to be collected from the shared platform, which was not completed in time and, hence, was not utilised when writing this thesis.

Specific questionnaires were completed in the presence of a carer or partner to reduce participants' tendency to conceal impulsivity symptoms. This method was applied to the self-rated Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease Rating Scale (QUIP-RS) and the Parkinson's Impulse Control Scale (PICS), which RF completed over the phone. Of note, ratings above 1 (from 0-4) to any questions on the QUIP-RS or disagreeing automatically triggered the administration of Parkinson's Impulsive Control scale (PICs). The PICs scale, therefore, was only administered for those patients who had rated one or more questions on the QUIP-RS >1 or whose family member/carer/partner rated one or more questions differently. Finally, those who did not score above 1 on any questions in the QUIP-RS nor had any rating disagreements were given the QUIP-RS again at the subsequent follow-ups to detect any changes. Carers were also invited to complete two scales, the Zarit Burden Interview (ZBI) and the European Quality of Life, 5 Dimension, 5 levels (EQ-5D-5L) at each time point, *Table* 12. Self-rated questionnaires were sent to participants at each point, but an over-the-phone interview for RF-rated questionnaires was arranged at the participants' convenience. As the interview could last 15-30 minutes, participants were recommended to take a break when necessary.

Table 13 Schedule and Method and Condition of Collectable Data

	Time Point(s)	***Duration***	***Location***	***Conditions***
Demography	Baseline	-	At local clinic	REC Approval Required

	Time Point(s)	*Duration*	*Location*	*Conditions*
PD duration	Baseline	-	At local clinic	REC Approval Required
DBS TARGET	Baseline	-	At local clinic	REC Approval Required
*DBS Parameters **	0-, 3-, 6-, 12-month time	-	At local clinic	REC Approval Required
Medications	0-, 3-, 6-, 12-month time	-	At local clinic	REC Approval Required
UPDRS PART III	0-, 12-month time	20 mins	At local clinic	REC Approval Required
UPDRS PARTS I, II, IV	0-, 6-, 12-month time	10 mins	Over Phone	REC Approval Required
QUIP-RS	0-, 3-, 6-, 12-month time	3 mins	At home	Required**
AES	0-, 3-, 6-, 12-month time	10 min	At home	Not Required
SHAPS	0-, 3-, 6-, 12-month time	10 mins	At home	Not required
PICs ϕ	0-, 3-, 6-, 12-month time	10 mins	Over Phone	Required
PDQ-39	0-, 3-, 6-, 12-month time	~ 10 mins	At home	required
EQ-5D-5L	0-, 3-, 6-, 12-month time	3 mins	At home	Required
NPI	0-, 3-, 6-, 12-month time	5 mins	Over Phone	Required
GAD 7	0-, 3-, 6-, 12-month time	2 mins	Over Phone	Not Required
PHQ-9	0-, 3-, 6-, 12-month time	2 mins	At home	Not Required
ZBI - Carer	0-, 3-, 6-, 12-month time	3mins	At home	Required
WSAS	0-, 3-, 6-, 12-month time	3 mins	At home	Not Required
UPPS-P	0-, 6- 12-month time	10 min	At home	Not required

***UPPS-P**= Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behaviour Scale, **MDS-UPDRS**= Movement Disorders Society Unified Parkinson's disease Rating Scale, **QUIP-RS**= Questionnaire for Impulsive-Compulsive Disorder in Parkinson's disease Rating Scale, **PDQ-39**= Parkinson's Disease Questionnaires-39 items, **EQ-5D-5L**= European Quality of life-5Dimensions-5Levels, **ZBI**=Zarit Burden Interview, **WSAS**= Work and Social Adjustment Scale, **AES**=Apathy Evaluation Scale, **PHQ-9**= Patient Health Questionnaire-9 items, **SHAPS**=Snaith-Hamilton Pleasure Scale, **PICS**= Parkinson's Impulse Control Scale, **GAD-7**= General Anxiety Disorder-7 items, **NPI-12**=Neuropsychiatry Inventory-12 items.*

**: DBS parameters include volts, pulse width, frequency, lead location, laterality, TEED and directionality, if available*

ϕ: This is done in each follow-up only for those who score above 1 in any of the questions on QUIP-RS

***: All scales and questionnaires that required permission to use were free.*

3.3.1.3 Eligibility Criteria

Patients

Inclusion criteria:

- Eligible and selected for DBS to treat motor symptoms of Parkinson's disease.
- English language fluency

Exclusion Criteria:

- Nil

Carers

Inclusion criteria:

- Someone who lives or/and looks after the patient
- English language fluency

Exclusion Criteria:

- Nil

3.3.1.4 Sample Size

The CRISP study was expected to recruit around 100 participants across the seven participating centres. Based on prevalence estimates from the literature, 20-25 % of this group would have a history of ICBs, have current mild ICBs or present with *de novo* ICBs at some point during the study (Baig et al., 2019; Liu et al., 2019). In previously published large trials of DBS, such as PDSURG (Weintraub et al., 2010), as well as large non-trial cohorts, ICBs were not specifically studied. Our sample size was expected to contain only a small number of participants who had or developed formally diagnosed ICBs. Nonetheless, a more significant number would be expected to experience or develop minor impulsive symptoms, which the QUIP-RS can detect. This thesis analysed the data as a consecutive case series since the study recruited 73 participants. If 100 participants were recruited as expected, this would give us an 80% power to detect a medium effect size on our primary outcome measures (QUIP-RS and PICs) (f^2=0.15) for the effect of 7 individual predictors at a significance level of 5%. This thesis used the SPSS software *29.0.1.0 (171)* to calculate the power for T0 and T2 for a medium Pearson and Spearman correlation effect size. For the Mann-Whitney and Wilcoxon sign rank, the effect size was calculated in Excel using ($r^2 = z^2/n - 1$) and $r = z/\sqrt{N}$, respectively. For t-tests, the SPSS provide effect size in a separate table, which is reported in the corresponding table.

3.3.1.5 Statistical Analysis Plan

All statistical analysis was performed using SPSS software *29.0.1.0 (171)*. Before commencing data analysis, a complete statistical analysis plan was created. Consultant statisticians at KCL/IOPPN guided the writing and implementation of the statistics plan. In this study, there was a concern about the risk of inadequate power; therefore, we did not use complete case analysis when dealing with missing data. Except for ICB-related data, all missing data were expected to be missing completely at random. The assumption was that some participants might skip sensitive questions on the ICB scales. In each case, the appropriate course of action was taken based on the reason for the lack of answers on each questionnaire (self-rated and clinician-rated) at each follow-up. In the observational study, data from across all variables was often missing, probably affecting the validity of the data. Among participants with active ICBs, a substantial number of participants may have been reluctant to report their symptoms. Therefore, to keep maximum statistical power, apart from dropping out for any reason, which is inevitable, a data collection and management plan were designed appropriately to reduce the possibility of having missing data in the following manner:

1- Follow-up schedules that were both strict and convenient.
2- Reminders of late collection or upcoming follow-ups both for LIs and participants
3- Timely follow-up with each participant to ensure required data has been collected.
4- Regular well-timed meetings between the chief investigator, RF and local investigators regarding follow-ups and data collection.
5- Timely follow-up for self-rated questionnaires which have not been returned
6- Stringent and transparent plans for data management

The normality of data distribution was assessed using the Shapiro-Wilk test and visual inspection of histograms. A summary of all characteristics is provided in a descriptive analysis at baseline. As some participants were recruited before the operation and others after the operation, a binary variable, "before and after the operation," was included. This variable was used to assess if impulsivity outcomes differed between the two groups and if the surgery procedure might have influenced outcomes.

As for Impulsive Compulsive Behaviours (ICBs), the QUIP-RS produced ordinal and continuous variables, i.e., total score and binary variables for cases that reach cutoff points. The same statistical analysis was executed for PICS. Where multiple statistical tests were

performed, a corrected or altered α Level was considered using the Bonferroni correction. This was mainly applied to individual ICDs (.05/4), UPDRS parts (.05/3), UPPS-P subscales (.05/5), stigma, emotional well-being, cognition subdimension of the PDQ-39 (.05/3) and the suicidality-related item on the PHQ-9 (0.5/2). All variables and their characteristics are presented in the table in the supplementary materials subsection. All *P* values were two-sided.

At baseline (T0), descriptive statistics are presented for all measured outcomes, including ICBs. This analysis is summarised in a single table for both time points (baseline and T2), including mean and standard deviation (SD). The percentage of participants (%) in each subgroup is presented in corresponding tables for categorical variables. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) and the Parkinson's Impulse-Control Scale (PICs) are two questionnaires used to assess impulsive compulsive behaviours (ICBs), which include Impulsive Control Disorders (ICDs) and other related impulsive behaviours. The in-depth analysis of ICBs relied on the results of the QUIP-RS as it is more widely used. However, the results of PICs are compared to those of the QUIP-RS to highlight the main differences in a separate section in *Chapter 5*. The ICDs that were assessed on both questionnaires are compulsive gambling, hypersexuality, compulsive shopping and binge eating. Other related ICBs assessed by both questionnaires include hobbyism, punding and dopamine dysregulation syndrome (DDS). The total scores of ICDs (ICDs total) on both questionnaires were a combination of the total scores on each ICD. The ICDs total and individual ICDs are analysed separately. The reason the ICDs total was additionally analysed is because in some studies impulsivity is reported as a single variable without specifying the behaviours (Santin et al., 2021). As for other related impulsive behaviours, the scores for hobbyism and punding were combined into one variable, while DDS was treated as a separate variable on both questionnaires. The research questions (H_0) regarding all ICBs are presented in *Table* 14. The difference in the frequency and severity of ICBs (QUIP-RS and PICs) were tested across the pre-defined age, gender, PD onset, LEDD median, retired, DA users and psychotropic use groups, *Table* 45. To illustrate, the PD onset subgroups were defined as early onset for the age below 50 at the time of PD diagnosis and late-onset for those above 50 (Mehanna et al., 2022; Schrag & Schott, 2006). Due to the normality of the distribution, the median of the total LEDD (> and <1103) was chosen to divide the cohort into two subgroups: above the median subgroup and below the median subgroup. The above vs below median represented the severity of the PD. To test the relation between the impulsivity

scores and usage of dopaminergic agents (DA), a binary variable was created based on the DA prescription (yes or no). To do further analysis based on the number of classes of PD medications that participants were prescribed, a binary variable was created under multi-PD medication users (≤2 *vs* ≥3). This decision was made because most participants take a combination of levodopa and a Type-B Monoamine Oxidase Inhibitors agent like Madopar or Sinemet, the most common PD treatment (Sivanandy et al., 2022). In addition, to investigate whether the frequency of positive cases of ICBs is higher in the retirement/not working subgroup, a binary variable was produced from an item on the Work and Social Adjustment Scale (WSAS). Three binary variables were created from the total score of depression (PHQ-9), anxiety (GAD-7) and apathy (AES) based on their corresponding cutoff points, *Table* 45. Subjects who scored beyond a certain cutoff point on each scale were considered to have clinically significant symptoms. Other groups are listed in the variables table under individual scales, *Table* 45. The Mann-Whitney *U* test was suitable for all analyses regarding the frequency difference of ICB-positive cases in pre-defined groups. Similar analyses were conducted for the ICDs total and each ICB on QUIP-RS and PICs.

Based on the asymmetric data distribution, Spearman's rank correlation coefficient was used to test if the ICDs total scores on the QUIP-RS correlate with other outcomes for which a cutoff point was not considered. This correlation model is less prone to extreme influential points, making it suitable for non-normality cases. The tests were conducted to investigate associations between the ICDs total (QUIP-RS and PICS) and PD duration, total levodopa equivalent daily dose (LEDD), neuropsychiatric symptoms on (NPI-12), quality of life on (PDQ-39), apathy (SHAPS & AES), sleep hours, UPDRS parts and UPPS-P and its subscales, as shown in *Table* 45. This analysis was primarily performed for questionnaires that did not have cutoff points for a specific neuropsychiatric symptom. For variables with symptom cutoff points, such as the GAD-7, associations were examined between impulsivity and the presence of clinical anxiety (cutoff=10). For related ICBs, the same analysis was repeated using the same test for age duration, age-at-operation, PDQ-39, NPI-12, SHAPS and UPDRS parts. This was done as the results of the ICDs total correlations with the above scales do not reflect their correlation.

For other psychiatric symptoms, comprehensive descriptive statistics are presented for the utilised scales and subscales. The Mann-Whitney U test was used to investigate the frequency difference in clinically significant psychiatric symptoms (including suicidality) and carer burden across gender, PD onset, LEDD median, employment status and recruitment time

groups. The Spearman correlation is used to analyse the correlation between the same set of variables in addition to the quality of life (EQ-5D-5L), the social and work adjustment (WSAS), and medication complication (UPDRS, IV) with PDQ-339, NPI-12, Sleep hours, the pleasure experiencing (SHAPS) and personality traits (UPPS-P). The research questions (H_0) regarding other psychiatric symptoms are presented in *Table* 15.

At T0, a regression model was used in a forward selection method to examine variables that are potential risk factors of scoring high for ICD total and individual ICBs, and frequency of multiple ICD cases. The examined potential predictive variables were informed by the narrative review presented in *Chapter 2*. All variables used in the analysis are listed in *Table* 47. The α level for variables that were items on the same scale was divided by their number to obtain a corrected α level indicating a significant regression coefficient. For example, for the UPPS-P 5 items, the α level was divided by 5. All variables were screened for significant outliers using the simple scatter plot. The outliner cases were identified via the case selection function and excluded while examining that variable.

The research questions (H_0) in *Table 16* are investigated in the second part of the data analysis at T2. The difference between T0 and T2 (the T0-T2 Difference) was analysed using the Wilcoxon sign rank test. The significant results were tested across pre-defined groups to look for any differences. The gender, PD onset, and working status groups were included in the tests. Before continuing to analyse changes (the T0-T2 difference) in ICBs, separate analyses had to be conducted to identify other psychiatric, quality of life, UPDRS, and personality traits variables that have significantly changed. This was essential before including them in the next step. Once identified, the correlation of their change in addition to age and PD duration was tested with the change in the ICBs, using Pearson correlation. The identified outcomes with significant change included LEDD, anxiety, PDQ-39, Apathy, EQ-VAS, UPDRS parts, UPPS-P and its subscales. A similar analysis was conducted using Pearson correlation for ICBs and personality changes.

The Paired sample *t*-test was used to test the change in PDQ-39, stigma (PDQ-39), Cognition (PDQ-39), EQ-VAS, UPDRS parts, Sleep hours, UPPS-P and subscales (except positive urgency). The Wilcoxon sign rank test was used to test the change in total LEDD, anxiety (GAD-7), Depression (PHQ-39), suicidality (item 9, PHQ-9), apathy (AES), NPI-12,

Psychosis (NPI-12), positive urgency trait (UPPS-P), Emotional well-being (PDQ-39), and the carer's burden (ZBI).

At T2, the same method was used to create a multilinear model. The variables listed in *Table* 47 were utilised to investigate their predictive potential for the change (T0-T2 difference) in the ICDs total and other significantly changed ICBs at T2. However, all tests for predictive factors were conducted while adjusting for the baseline score of the ICDs total and individual ICBs. Baseline scores were adjusted for in the multiple regression to decrease the variability between participants and, hence, to increase the power of the analysis (Bland, 2015; Hu et al., 2022; Santin et al., 2021). In addition, reducing variability reduces multicollinearity, which results in the relative increase in accuracy and improves the regression model (Kim, 2019).

Lastly, *de novo* cases of impulsivity were identified using 'select cases' function on the SPSS. To illustrate, using 'select cases' in SPSS, only cases who did not score above the corresponding cutoff points for the ICDs total and individual ICBs at T0 were selected. Then a new variable was created in which selected cases that scored above the cutoff point at T2 were coded as *de novo* cases. Mann Whitney *U* test was used to investigate difference in characters and main outcomes between *de novo* ICBs cases and non-*de novo* cases.

Table 14 Research Questions at T0 For ICBs

Variables	**Research Questions (H_0)**
Gender	ICBs are not associated with gender.
PD Duration	ICBs are not associated with PD duration.
Early-onset	ICBs are not associated with early-onset PD.
Retired/nonworking	ICBs are not associated with not working.
LEDD	ICBs are not associated with higher LEDD.
DAs	ICBs are not associated with higher DA.
Psychotropic	ICBs are not associated with higher Psychotropic (psychiatric comorbidities).
Apathy	ICBs are not associated with Apathy.
Depression	ICBs are not associated with depression.

Variables	Research Questions (H_0)
Anxiety	ICBs are not associated with anxiety.
Work and social life	ICBs are not associated with clinically impaired work and social life adjustment.
PDQ-39	ICBs are correlated with PDQ-39 total score.
NPI-12	ICBs are correlated with the NPI-12 total score.
UPPS-P	ICBs are correlated with Personality traits.
UPDRS, I	ICBs are correlated with UPDRS, I total score.
UPDRS, II	ICBs are correlated with UPDRS, II total score.
UPDRS, IV	ICBs are correlated with UPDRS, IV total score.
Individual ICBs	Predictors of ICBs at baseline.
Multi ICDs	Predictors of cases of multi ICDs at baseline.

Table 15 Research Questions at T0 Other Psychiatric Symptoms, Quality of Life, Work and Social Adjustment and Carer Burden

Variables	Research Question (H_0)
	Depression (PHQ-9)
Gender	Depression is not associated with gender.
Early onset	Depression is not associated with early onset.
Retired/nonworking	Depression is not associated with not working.
Recruitment time	Depression is not associated with recruitment after operation.
PD duration	Depression is associated with PD duration.
LEDD	Depression is not associated with higher LEDD.
NPI-12	Depression is not associated with higher NPI-12.

Variables	Research Question (H_0)
PDQ-39	Depression is not associated with higher PDQ-39.
WSAS	Depression is not associated with work and social impairment.
	Anxiety (GAD-7)
Gender	Anxiety associated with gender.
Early onset	Anxiety associated with early onset.
Retired/nonworking	Anxiety associated with being not working.
Recruitment time	Depression is not associated with recruitment after operation.
PD duration	Anxiety associated with PD duration.
LEDD	Anxiety associated with higher LEDD (more severe PD).
NPI-12	Anxiety associated with NPI-12.
PDQ-39	Anxiety associated with PDQ-39.
WSAS	Anxiety is not associated with work and social impairment.
	Apathy (AES)
Gender	Apathy is not associated with gender.
Early onset	Apathy is not associated with Early-onset.
Retired/nonworking	Apathy is not associated with not working.
LEDD	Apathy is not associated with lower LEDD.
Anxiety	Apathy is not associated with anxiety (GAD_7).
Depression	Apathy is not associated with depression (PHQ-9).
NPI-12	Apathy is not associated with NPI-12.
PDQ-39	Apathy is not associated with PDQ-39.

Variables	Research Question (H_0)
WSAS	Apathy is not associated with work and social impairment.
	Carer burden (ZBI)
Gender	The higher burden is not associated with the gender of the patient.
Early onset	Higher burden is not associated with early onset.
Retired/nonworking	A higher burden is not associated with not working.
LEDD	The higher burden is not associated with LEDD.
Impulsivity	The higher burden is not associated with the total score on QUIP-RS.
	The higher burden associated with the total score on PICS.
Treatment complications (UPDRS, IV)	The higher burden is not associated with IV.

Table 16 The Research Question at T2 For ICBs

Variables	Research Questions (H_0)
The ICDs total (QUIP-RS)	The ICDs total remains unchanged after STN-DBS.
Compulsive gambling	Compulsive gambling remains unchanged after STN-DBS.
Hypersexuality	Hypersexuality remains unchanged after STN-DBS.
Binge eating	Binge eating remains unchanged after STN-DBS.
Compulsive shopping	Compulsive shopping remains unchanged after STN-DBS.
Hobbysm-Punding	Hobbysm-Punding remains unchanged after STN-DBS.
DDS	DDS remains unchanged after STN-DBS.
De novo ICDs	The STN-DBS does not cause *de novo* ICDs
De novo Hobbysm-Punding	The STN-DBS does not cause *de novo* Hobbysm-Punding

Variables	**Research Questions (H_0)**
De novo DDS	The STN-DBS does not cause *de novo* DDS
Gender	ICBs T0-T2 differences are not associated with gender.
PD Duration	ICBs T0-T2 differences are not associated with PD duration.
early onset	ICBs T0-T2 differences are not associated with early-onset PD
Retired/nonworking	ICBs T0-T2 differences are not associated with not working.
LEDD	ICBs T0-T2 differences are not associated with higher LEDD.
Apathy	ICBs T0-T2 differences are not associated with the T0-T2 difference of Apathy.
Depression	ICBs T0-T2 differences are not associated with the T0-T2 difference in depression.
Anxiety	ICBs T0-T2 differences are not associated with the T0-T2 difference in anxiety.
PDQ-39	ICBs T0-T2 differences are not associated with the T0-T2 difference of PDQ-39 total score.
NPI-12	ICBs T0-T2 differences are not associated with the T0-T2 difference of NPI-12 total score.
UPPS-P	ICBs T0-T2 differences are not associated with the T0-T2 difference of UPPS-P total score.
UPDRS, I	ICBs T0-T2 differences are not associated with the T0-T2 difference of UPDRS, I total score.
UPDRS, II	ICBs T0-T2 differences are not associated with the T0-T2 difference of UPDRS, II total score.
UPDRS, IV	ICBs T0-T2 differences are not associated with the T0-T2 difference of UPDRS, IV total score.
Sleep hours	ICBs T0-T2 differences are not associated with the T0-T2 difference in Sleep hours.

Table 17 The Research Question at T2 for Other Psychiatric Symptoms, Quality of Life, Work and Social Adjustment and Carer Burden

Variables	**Research Questions (H_0)**
Anxiety	Anxiety remains unchanged after STN-DBS.
Depression	Depression remains unchanged after STN-DBS.
Psychosis	Psychosis remains unchanged after STN-DBS.
Stigma	Stigma remains unchanged after STN-DBS.
Emotional Well-being	Emotional Well-Being remains unchanged after STN-DBS.
Cognition	Cognition remains unchanged after STN-DBS.
Quality of life (PDQ-39 +EQ-VAS)	Quality of life remains unchanged after STN-DBS.
Carer burden	Carer burden remains unchanged after STN-DBS.

3.3.2 Patient and Public Involvement (PPI)

The CRISP study was reviewed by a group with experience in mental health problems and their carers, who have been specially trained to advise on research proposals and documentation. This was arranged through the Feasibility and Acceptability Support Team for Researchers (FAST-R), a free, confidential service in England provided by the National Institute for Health Research Maudsley Biomedical Research Centre via King's College London and South London and Maudsley NHS Foundation Trust (See *Appendix 15*)

The study was also presented to a PD lay advisory group of patients and carers linked with the DBS UK network. We also discussed the study with several expert patients at King's, who are part of a local support group. We met with Parkinson's UK (the main UK patient charity) and shared the protocol with them, taking on board any comments. The study was also shared with all centres in the UK DBS network, including those not participating. We plan to engage with the charity Parkinson's UK to assess study results and discuss and disseminate findings.

3.3.3 Funding and Supply of Equipment

The study funding was reviewed by the SLaM R&I office and was deemed sufficient to cover the study requirements.

1- The UK DBS registry was already active before the study and was provided by Orion MedTech. Orion MedTech did not require extra funding to cover the costs of the research shared database prototype. The CRISP study did not utilise the UK DBS registry.
2- As a research fellow, AA was employed on an honorary contract at SLAM to carry out research. AA was trained by senior staff in the application of rating scales and registered for a self-funded PhD at KCL/IoPPN; therefore, no additional budget was required.

3.3.4 Data Handling and Management

The local principal investigator (PI) at each site was responsible for archiving all research data in an assigned cabinet to allow the research team to access it at any time. The data collected by the RF was archived in designated SLAM office space in lockable drawers. All data was saved in password-protected documents. Furthermore, all data was anonymised on paper and in soft copy.

3.3.5 Peer and Regulatory Review

This study was peer-reviewed by experts external to the research team under the supervision of the SLAM R&D office. The Research Ethics Approval form was submitted through the IRAS online service (IRAS project ID: 285162). The West London & GTAC Research Ethics Committee (REC Reference: 21/LO/0580) reviewed and granted approval for the study (See *Appendix 12*).

3.3.6 Protocol Deviations and Notification of Protocol Violations

A deviation is defined as an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI monitored protocol deviations.

A protocol violation is defined as a breach which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

The CI and R&I Office were notified immediately of any case where the above definition applied during the study conduct phase. At least two substantial (significant) amendments and two non-substantial (minor) amendments were requested and approved to date (Nov. 2023). The significant substantial amendments were to extend the baseline recruitment window to after the operation (but prior to DBS activation) and extend the last recruitment date to Dec 2024 (See *Appendix* 10). The minor amendments were limited to adding or changing research members at individual participating centres (See *Appendix* 11). Other deviations were reported immediately to the CI, and appropriate action was taken accordingly. For example, an error was made in the WSAS questionnaire. The questionnaires should have asked participants, "How Parkinson's disease has impacted your work and life…" but instead, mistakenly, Parkinson's disease was replaced by impulsive behaviours. For participants whose data collection window at the time point was not closed, the error was rectified by calling them and completing the questionnaire again. For the remaining participants, the WSAS was disregarded in the current analysis. However, the scale remains in the database and is identified via a variable specifying whether the WSAS was administered for PD or impulsive behaviours.

3.3.7 Monitoring and Auditing

The Chief Investigator was responsible for the ongoing management of the study. The Sponsor was obligated to monitor and conduct audits on a selection of studies in its clinical research portfolio. Monitoring and auditing were to be conducted in accordance with the UK Policy Framework for Health and Social Care 2017 and in accordance with the Sponsor's monitoring and audit procedures. The CRISP study has not been selected for audit by the Sponsor.

3.3.8 Training

The Chief Investigator reviewed and provided assurances regarding the training and experience of the RF in this study. Appropriate training records are maintained in the study files. The senior staff, including the CI, trained the RF in applying rating scales.

3.3.9 Intellectual Property

All intellectual property rights and know-how in the protocol and the results arising directly from the study, excluding all improvements thereto or clinical procedures developed or used

by each participating site, shall belong to the SLaM NHS Trust. Each participating site agreed that by approving to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to SLaM and to disclose all such know-how to SLaM with the understanding that they may use the know-how gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of SLaM confidential information or infringement of the SLaM IPR.

3.3.10 Indemnity Arrangements

The SLaM NHS Indemnity held insurance against claims from participants for harm caused by their participation in this clinical study. Participants could claim compensation if they could prove that a participating centre has been negligent. Each site covered any negligence from their staff as part of the conduct policy at their site.

3.3.11 Publication and Dissemination Policy

The results of this study had not been published at the time of thesis submission. However, the preliminary results had been presented at conferences and meetings. A poster of the preliminary results presented by A.A. at the neuropsychiatry conference at the Royal College of Psychiatrists won the 2nd prize in the Trainee/SAS Doctor Poster Prize competition. A.A. has also presented a poster at an international conference in Grenoble/France and other staff and student meetings at the IOPPN. The CI, D.O., has presented the preliminary results at the UK DBS network. The study results will be reported and disseminated at international conferences and in peer-reviewed scientific journals. Results will be published as soon as sufficient data is collected and analysed. The aim is to publish results after sufficient participant data is collected at a minimum 3-month follow-up. The results will be published as a case series if enough participants are not recruited. In addition, local PIs may present results at local academic and clinical meetings and the UK DBS Network meetings.

3.3.12 Materials

The following rating scales were used in the CRISP study to be completed by the RF or patient/carer, as shown in *Figure* 11 and were added to the registry by the RF.

3.3.12.1 The Scales and Questionnaires

1- **Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease Rating Scale (QUIP-RS):** This uses a 5-point Likert scoring to measure the frequency and severity

of seven ICBs (Weintraub et al., 2012). As explained before, impulsive control disorders (ICDs) are referred to as the first 4 impulsive compulsive behaviours (ICBs) measured on the QUIP-RS. They are the most common ICDs in PD and include compulsive gambling, hypersexuality, compulsive shopping and binge eating. ICBs is an umbrella term including the 4 ICDs and other related impulsive compulsive behaviours (ICBs) (hobbyism, punding and DDS) measured on the QUIP-RS (Ávila et al., 2011). Therefore, when referring to hobbyism, punding and DDS, "other related ICBs" was used. However, ICBs or impulsive behaviours[22] were used when referring to combined ICDs and other related ICBs.

The QUIP-RS is a self-rated questionnaire. Participants answered 4 questions for each of the seven ICBs. These 4 questions cover thought, urge, difficulty controlling, and problematic behaviours associated with each ICB. It has been recommended as a diagnostic screening tool for ICBs (except DDS) and their severity by the International Parkinson's and Movement Disorder Society (Evans et al., 2019). In addition, the scale has been validated in the population of other languages, such as German and Brazilian Portuguese (Guerra et al., 2020; Probst et al., 2014). Previously, another version of this scale, the Questionnaire for Impulsive-Compulsive Disorder in Parkinson's disease (QUIP), operated with a dichotomous option in which patients could only choose 'yes' or 'no'. However, the newer QUIP-RS provides information about the severity of symptoms under the question. Compared with the QUIP, the QUIP-RS is superior in identifying subsyndromal symptoms and monitoring changes over time. The authors have reported good specificity and sensitivity and a good interrater and retest reliability of >0.90 for ICDs and 0.68 and 0.77 for hobbyism-punding combined and DDS, respectively (Weintraub et al., 2012). Regarding hobbyism and punding scores, their total scores are combined and dealt with as a single variable in this thesis. The ICDs were analysed individually and combined to create the 'ICDs total score'. Furthermore, the cutoff[23] for individual ICDs, 'total ICDs', and other ICBs were based on the reports of the authors of QUIP-RS, which ensures the specificity and sensitivity exceed 80%. It should be noted that these cutoff points may vary across cohorts and nations for individual ICDs, as researchers reported in a consecutive case series study of Japanese PD patients (Takahashi et al., 2022). The cutoff point for 'ICDs total

[22] In the literature, they are sometimes referred to as problematic behaviours(K. Wu et al., 2014).

[23] Cut-off is an alternative spelling in the literature.

score' is ≥10, but the cutoff points are different for individual ICDs: compulsive gambling: ≥6, hypersexuality: ≥8, binge Eating: ≥7, compulsive shopping: ≥8. In addition, the cutoff point for the combined scores of hobbyism and punding is ≥7. As for DDS, as the creators of the scale have not provided any cutoff, other studies recommended a score above 6. Lastly, the ratings may differ between an informant and a patient (Evans et al., 2019; Weintraub et al., 2012). Therefore, in the CRISP study, participants were advised to complete the QUIP-RS with their carer/partner/relative and report any discrepancies. This was done to minimise the impact of such differences in the ratings.

Strengths: Time- and cost effective. Assessment of severity, frequency and change over time. Valid and reliable among PD patients.

Weakness: The cutoff points for other ICBs were taken from a specific cohort and may not be generalisable to other populations. They have not been validated in DDS. The scale is self-rated and does not measure the psychosocial impact of impulsive behaviours.

2- Parkinson's Impulsive Compulsive Scale (PICS)

Patients may not recognise or complain about the impulse behaviour due to a lack of insight (Claes et al., 2005). Some patients may even try to conceal either the behaviours or their severity (Papay et al., 2011). Hence, self-rating scales such as the QUIP-RS may not always be enough to screen for impulsive behaviours. Moreover, given the negative impact of ICBs on patients' and their relatives' social and occupational lives (Merner et al., 2023), the PICS, as a multidimensional approach, was developed to help clinicians assess ICBs more thoroughly (Okai et al., 2016). The participants are asked if they have experienced each of the 7 ICBs in the past months. The screening and the rest of the interview are conducted over the phone with a carer present, if possible. The questions are written with the sensitive nature of behaviour in mind.

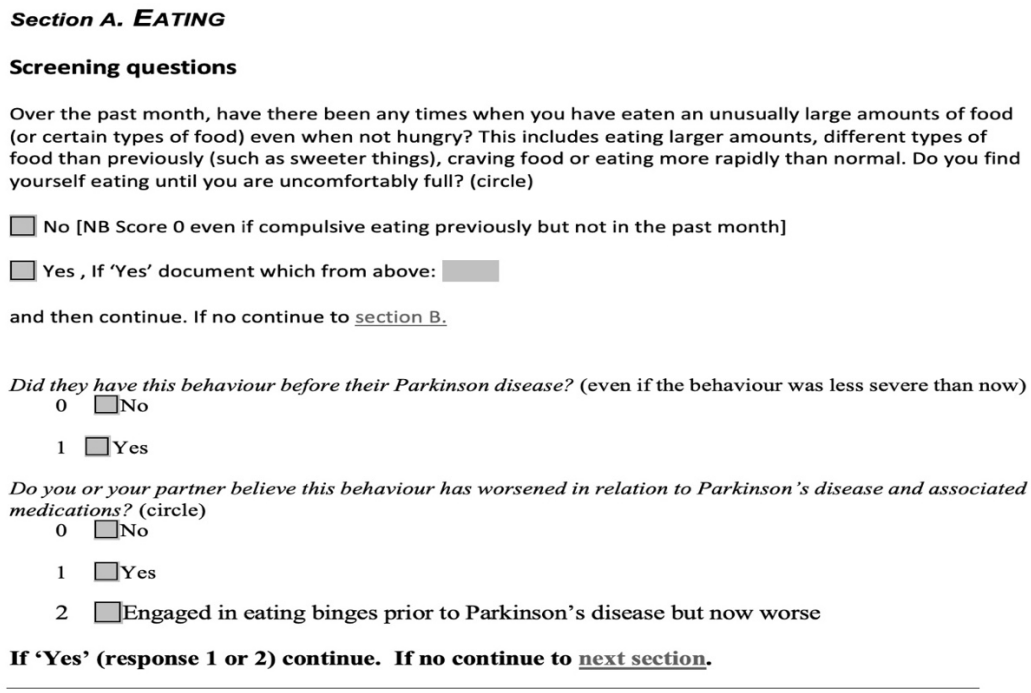
As shown in *Figure* 12, other ways the ICBs may be expressed are also questioned during the screening phase. Once a participant answered positively to a screening question, other questions follow to gather sufficient insight about the severity and the socioeconomic impact of the behaviours. On the PICS, the severity of individual ICBs is measured by combining their intensity and psychosocial impact. Compared to the QUIP-RS, which measures the severity by asking directly about the intensity of urges, thoughts, control, and problematic behaviours associated with impulsive behaviours, the PICS asks for more specific details about each positive ICB to assess the severity and its psychosocial impact.

For example, for gambling, it asks the subject about the frequency and size of the bets lost and won. It also asks if they have borrowed money to bet, if their relatives have expressed concern, etc. These questions help the interviewer to know the intensity and social impact of the individual impulsive behaviours. Another advantage of the PICS is that once a patient has said 'yes' to a screening question, for example, "eating too much sweet food" under the binge eating section, in a follow-up question, they are immediately asked if they have always had this behaviour and if it has got worse with PD and its medications. If the patient's answer is 'yes' to the first question and 'no' to the second follow-up question, then no further assessment is conducted for binge eating, and the interviewer skips to the next question. Meanwhile, in the QUIP-RS, this differentiation cannot be made. Therefore, the PICS focuses only on PD-related impulsivity, which may be reflected in the results.

The scale's authors have provided a preliminary clinical cutoff point for each behaviour to be 4-5/12. The scale is responsive to change over time and has an acceptable reliability (Okai et al., 2016). This thesis utilised the author's suggested cutoff point for ICDs' total score =6, the rounded score of 6.6 presented in the authors' report with a sensitivity above 90% (Okai et al., 2016). A score of 6 was chosen instead of 7 to favour the scale's sensitivity. The same was applied for cutoff points of individual ICDs on the PICS: binge eating = >3, hypersexuality=>2, compulsive gambling =>4, and compulsive shopping >3, with sensitivities above 80% (Okai et al., 2016). As for other related ICBs (Hobbysm + Punding and DDS), a cutoff point 4 is considered to improve sensitivity. The scores for hobbyism and punding were combined to produce a single variable to unify variables across both ICB scales used in the data analysis. The PICS has been classified as a "suggested" scale for diagnostic screening and severity rating by the International Parkinson's and Movement Disorder Society (Evans et al., 2019). Given the recent development and limited use of ICBs in PD, the CRISP Study will produce more data on this promising scale to help better understand its psychometric properties. The RF underwent two training sessions with the scale author and chief investigator of the CRISP Study, D.O., to acquire the necessary skills to conduct the interviews.

Strengths: Semi-structured clinician-rated tool. Measures severity frequency and considers the psychosocial impact.

Weakness: It can take over 20 minutes if there is more than one positive ICB. It has not been widely utilised in other PD cohorts, and its psychometric properties will need further confirmation.



Section A. EATING

Screening questions

Over the past month, have there been any times when you have eaten an unusually large amounts of food (or certain types of food) even when not hungry? This includes eating larger amounts, different types of food than previously (such as sweeter things), craving food or eating more rapidly than normal. Do you find yourself eating until you are uncomfortably full? (circle)

☐ No [NB Score 0 even if compulsive eating previously but not in the past month]

☐ Yes , If 'Yes' document which from above:

and then continue. If no continue to section B.

Did they have this behaviour before their Parkinson disease? (even if the behaviour was less severe than now)

0 ☐ No

1 ☐ Yes

Do you or your partner believe this behaviour has worsened in relation to Parkinson's disease and associated medications? (circle)

0 ☐ No

1 ☐ Yes

2 ☐ Engaged in eating binges prior to Parkinson's disease but now worse

If 'Yes' (response 1 or 2) continue. If no continue to next section.

Figure 12 An Example of Screening Questions in PICs

3- **The Neuropsychiatric Inventory (NPI-12)**: This was initially developed to assess patients with dementia (Cummings, 1997); however, it is frequently used to assess the presence and severity of comorbid psychiatric disorders in PD patients. (Aarsland et al., 2007). Of note, the use of the NPI-12 in PD has been well-validated (Aarsland et al., 1999). The NPI-12 version, used in the CRISP study, covers sleep and eating in addition to the 10 psychiatric symptoms covered in the original version (Kaufer et al., 2000). Therefore, it includes 12 different symptoms: Delusions, Hallucinations, Agitation/Aggression, Depression, Anxiety, Elation/Euphoria, Apathy/Indifference, Disinhibition, Irritability, Aberrant motor behaviour, Sleep and nighttime Behaviour Disorders, Appetite and Eating Disorders. It is noteworthy that NPI-12 focuses on the behavioural and somatic effects of symptoms under question (Leentjens et al., 2008a). RF administers it over the phone to an informed carer, preferably one who lives with the participant. The symptom frequency ranges from 1 to 4, and the severity ranges from 1 to 3. The multiplication of frequency and severity determines a composite score for each symptom, ranging from 1 to 12. To calculate the NPI-12 total

score (0-144), it is necessary to sum up all the composite scores. A cutoff point was not considered in this thesis. Instead, the total and subscale scores were analysed before and after the operation. This is because a cutoff score for the PD population has not been proposed (Leentjens et al., 2008a), and any score above 1, especially for delusion and hallucinations, will only warrant further investigation (Hansen et al., 2019). It is recommended to use more specific instruments to assess individual symptoms, such as visual hallucinations (Holiday et al., 2017). Nonetheless, it remains a valuable tool for reporting changes in total scores or subscales (Saari et al., 2022).

Strengths: Reliability, time efficiency, and cost-effectiveness.

Weakness: No cognitive assessment. Not much reliability for sub-questions.

4- **Generalised Anxiety Disorder -7 (GAD-7)**: This is a 7-item screening and severity assessment tool for generalised anxiety disorder (Spitzer et al., 2006). It has shown good discriminant validity and reliability among large cohorts (Johnson et al., 2019). It has been frequently used for PD and DBS-PD (Achey et al., 2018). However, its accuracy in PD has not been measured compared to other available scales (Dissanayaka et al., 2015; Martinez-Martin et al., 2016). Recently, Parkinson's Anxiety Scale (PAS) was released, which is disease-specific and brief, but reports on its clinimetric properties were not available at the time (Schneider et al., 2022). Therefore, because it is a brief and easy-to-complete screening tool, the GAD-7 is deemed suitable for a study like the CRISP study in which participants are mainly older and are undergoing an invasive operation. In addition, despite the availability of other validated instruments for anxiety, the GAD-7 was chosen because it was free for student-based studies and did not require paperwork during times like the pandemic when obtaining permission was unusually time-consuming.

   The seven questions on the GAD-7 evaluate feeling nervous, anxious, or on edge, having the ability to stop or control worrying, being overly anxious about various things, trouble relaxing, restlessness, irritability, and feeling anxious about the possibility of occurrence of a terrible event. In addition, the creator of the GAD-7 reported that in the general population, a cutoff point >10 indicates the clinical significance of anxiety (Spitzer et al., 2006). In this thesis, the exact cutoff point is considered.

   Strength: Cost and time effectiveness. Reliability in the general population.

   Weakness: Despite being used frequently, there are fewer reports on its reliability in PD cohorts. Recent anxiety related to the operation is not differentiated from chronic anxiety.

5- **The Patient Health Questionnaire-9 Items (PHQ-9)**: This self-administered diagnostic instrument screens for depression and takes about 2 minutes to complete (Kroenke & Spitzer, 2002). The instrument has been validated for criteria-based diagnosis of depression among a large cohort (Spitzer et al., 1999). The authors have reported that PHQ-9 is also sensitive to change over time (Kroenke & Spitzer, 2002). Despite the availability of instruments with preferable psychometric properties among PD patients, e.g., the Geriatric Depression Scale-15 (GDS-15), the PHQ-9 is considered more suitable because it focuses on somatic symptoms of depression. The somatic symptoms of depression can make depression diagnosis more difficult in PD (Hoogendijk et al., 1998; Thompson et al., 2011). In addition, compared to the Structured Clinical Interview for the fourth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-IV) depression module (SCID), the PHQ-9 is more sensitive to pain-related depressive symptoms (Thompson et al., 2011), another common feature of depression among PD (Mylius et al., 2021). Therefore, the PHQ-9 remains an adequate questionnaire for screening depression in PD. In this thesis, the total score was used in our data analysis to report any change in depression over time. In addition, to indicate clinically significant depression, a score equal to or greater than 9 (0-27) is considered as the cutoff point (Chagas et al., 2013). Suicidal ideation was also screened for in addition to depression. The PHQ-9 suicidal ideation and attempt item (the last question) is shown in studies with large cohorts to be a strong predictor of suicidality (Rossom et al., 2017). As item 9 on the PHQ-9 screens for suicidality and is an ordinal categorical variable, a binary variable with a cutoff point of 1 is considered for suicidality. Like other selected questionnaires, completing the PHQ-9 was also easier and more effective for the cohort of the CRISP study.

   Strength: It is brief and cost-effective. Its validity in PD patients is reported.

   Weakness: It has a lower specificity compared to alternatives. The focus is on somatic symptoms and less on cognitive symptoms of depression.

6- **Snaith-Hamilton Pleasure Scale (SHAPS)** (Snaith et al., 1995) **and Apathy Evaluation Scale (AES)** (Marin, 1991)**:** The two scales measure anhedonia and apathy, respectively. Anhedonia refers to the inability to experience pleasure and is a primary symptom of major depressive disorder (Antosik-Wójcińska et al., 2017a). It is defined by the fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-V) as '**markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly**

every day' (Kaji & Hirata, 2011a). That said, anhedonia may not always be explained by depression among PD patients. Like apathy, it responds to specific dopamine agonists (DAs) and may develop after withdrawal of DAs (Leentjens et al., 2008; Loas et al., 2012). Like depression and apathy, anhedonia may also result from a reduction of dopaminergic agents after DBS (Antosik-Wójcińska et al., 2017a). Furthermore, knowing that, like apathy and suicide, anhedonia has also been reported to be associated with depression (Doshi et al., 2020) and dopamine reduction or withdrawal (Nirenberg, 2013), it should be assessed to gain a better understanding of it.

In clinics, differentiating anhedonia, apathy, and depression can be challenging. This thesis measured anhedonia as a distinct variable (SHAPS) to see how it related to other psychiatric symptoms and variables. Anhedonia differs from apathy in that the patient's sensitivity to pleasure is decreased, while there is a lack of primary motivation in apathy. However, apathy can also manifest as decreased willingness and emotional disturbances, which have been reported as symptoms of anhedonia in PD. Also, a meta-analysis of 23 studies (n>5000) revealed that more than half of PD patients suffering from apathy were suffering from concomitant depression. This finding supports the notion that apathy is a distinct morbid state that may have overlapping symptoms with depression (den Brok et al., 2015; Lueken et al., 2017). Consistently, patients with apathy exhibited significant anhedonia in a small cohort (n=45)(Pluck & Brown R, 2002). In fact, apathy and anhedonia are believed to be the outcomes of a disturbance in the dopamine reward system (Kaji & Hirata, 2011a). Therefore, it can be challenging to differentiate between apathy and anhedonia clinically. Experts from around the globe propose the following criteria to diagnose apathy in PD: A reduction or lack of emotion, goal-driven behaviour, and goal-directed cognitive activity and motivation, with at least one of the former three criteria, must be reported for at least 4 weeks for the majority of that time (De Waele et al., 2022). The use of the AES as a screening test for apathy in PD has been validated (Lueken et al., 2017). The AES is comprised of 18 items that are scored on a 4-point Likert scale. Items are scored between 1 and 4, and three inverted items are recorded once reversed (items 6, 10, and 11). The higher the score, the greater the apathy (18–72). A cutoff point of >38 has been suggested to reflect the presence of clinically significant apathy, with some evidence of sensitivity to change after DBS (Drapier et al., 2006) and methylphenidate (Andrade, 2022). The AES allows for a valid assessment of apathy as a distinct syndrome (den Brok et al., 2015).

Despite having the UPDRS item 4 as a recommended screening test for apathy (Leentjens et al., 2008), using the AES is essential, especially in research settings, as the former does not distinguish between depression and apathy-induced lack of motivation (Pedersen et al., 2008). However, it must be noted that the AES is not a replacement for a formal clinical interview.

The SHAPS is also a widely used screening tool in PD cohorts for anhedonia assessment and is shown to be sensitive to change following treatments (Leentjens et al., 2008). For the SHAPS, a cutoff point of 2 is considered to report the presence of anhedonia (Snaith et al., 1995). Therefore, the SHAPS and AES can be integrated into a model that can evaluate the impact of DBS on both combined and distinct morbid states. Although both apathy and anhedonia were measured briefly by other scales in this study, the AES and SHAPS were used to allow investigation as separate psychiatric symptoms and also to allow examination of their association with other outcomes. To make it easier for participants to complete the scales, their respective authors have shortened both without affecting their validity (Kaji & Hirata, 2011a).

Strength: Both scales have acceptable specificity and sensitivity among PD patients. Both are time and cost-effective.

Weakness: Both scales require further validation among PD cohorts.

7- **Parkinson's Disease Questionnaires – 39 Items (PDQ-39):** This is a self-reported questionnaire that addresses various aspects of functioning and well-being in PD (Peto et al., 1995). It takes about 10 minutes to complete. There are 39 questions on the PDQ-39, covering 8 distinct domains: mobility (10 questions), activities of daily living (6 questions), emotional well-being (6 questions), social support (3 questions), stigma (4 questions), cognitions (4 questions), communication (3 questions) and bodily discomfort (3 questions). The PDQ-39 is a validated tool to assess the impact of the disease or treatments (like DBS) on each subscale, i.e., a particular aspect or on the sum of their scores, i.e., the summary index, as an indicative of patients general functioning and well-being (Jenkinson et al., 1997). The summary index is calculated by adding scores of all 8 dimensions and dividing it by 8. Its authors reported that it significantly correlates with other PD severity assessment tools, like the Hoehn and Yahr staging scale (Hoehn & Yahr, 1967; Jenkinson et al., 1997). Of interest, a more recent multicentre, cross-sectional study in Italy reported that it is possible to determine the stage of PD on Hoehn and Yahr staging scores using the PDQ-39

summary index (Galeoto et al., 2022). To illustrate, a PD patient with a cutoff point of <32.5 on the PDQ-39 summary index can be in the first stage of the disease on the Hoehn and Yahr staging scale with a sensitivity of 83% and specificity of 81%. The authors have also demonstrated that age and gender make a difference in such correlations. The subscores for stigma (Ma et al., 2016), cognition and emotional well-being (Jones et al., 2014; Schönenberg & Prell, 2022) have also been reported to have the convergent validity and internal consistency of other validated scales. Although the summary index and any change over time were reported in this thesis, the subscores for each measured dimension are discussed separately. The main reason is that two individuals with similar PDQ-39 summary indexes may not be clinically comparable. That is to say, the summary index is not supported to represent a unidimensional construct (Hagell & Nilsson, 2009).

Strength: Valid and widely used questionnaire. Measures 8 different dimensions in patients' quality of life.

Weakness: It takes about 10 minutes to complete. The PDQ-39 summary index does not specify the similarities or differences between participants in various domains.

8- **The Zarit Burden Interview-12 Items (ZBI-12):** This is a self-administered scale (by a carer) to measure the carer's burden (Zarit et al., 1980). The scale was administered only if a participant's carer agreed to participate in the study. Otherwise, this scale was omitted for that participant. The ZBI-12 has been approved for PD studies focusing on the carer burden (Hagell et al., 2017). It has also been used in studies investigating the impact of ICBs on the carer burden (Leroi et al., 2012a). In a cross-sectional study of 149 PD patients exploring the disease burden on carers, the ZBI-12 strongly correlated with carers' PHQ-9 and GAD-7 and patients' total score on the global assessment of functioning scale (GAF)(Ballesteros et al., 2012; Yu et al., 2018). For the 12-item version of ZBI in a cohort with minimal cognitive impairment, a cutoff point of 17 was deemed safe to divide the low and high burden. However, this is not to be considered normative data (Bédard et al., 2001; Stagg & Larner, 2015). Furthermore, a cutoff point 17 has been frequently used in other PD-DBS studies (Carrilho et al., 2018; van Hienen et al., 2020). However, additional investigation into the psychometric properties of the current version is necessary for PD patients.

Strength: Time and cost-effectiveness. Validity and reliability are approved for the current shorter version.

Weakness: The short version lacks information on psychometric properties for PD cohorts. It does not provide information about the demographics and comorbidities of carers

9- **The European Quality of Life Questionnaire- 5 dimension- 5 level (EQ-5D-5L):** The importance of quality of life (QoL) in health care is growing. Therefore, in addition to the PDQ-39, another validated questionnaire produced to measure QoL is the EQ-5D-5L (Schrag et al., 2000). Only five questions and a visual analogue scale (EQ-VAS) are included in this short questionnaire. It is both easy to complete and appealing to elderly populations. The EQ-5D-5L health states may be converted into a single index value. Quality-adjusted life years (QALYs) can be calculated using the index values. Economic evaluations of healthcare interventions are based on QALYs. Although the single value index will be included in the CRISP study publications, in this thesis, only results from the EQ-VAS are reported and utilised in analyses, as it validated and shown to have moderate correlation with other QoL instruments such as the PDQ-39 and Movement Disorders Society Unified Parkinson's disease Rating Scale (MDS-UPDRS) among PD patients (Alvarado-Bolaños et al., 2015).

   Strength: Validity of EQ-VAS, Easy to complete.

   Weakness: Many studies employ other versions, which could result in inconsistent findings.

10- **Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)**: This scale is a new edition of the original UPDRS developed in 1980 (Goetz et al., 2008). The UPDRS now has refined scoring guidelines and descriptions. In addition, impairments and disabilities associated with milder signs and symptoms receive special attention (Lang et al., 2013). Part I covers non-motor daily living experiences, Part II covers motor daily living experiences, Part III covers a motor examination, and Part IV covers motor complications. Although all parts were collected for the CRISP study, for this thesis part, III was not included as it is completed by local teams and archived locally. The lack of staff and time made it impossible to include the results of part III for all participants from all seven participating centres. The UPDRS III will be collected for the final analysis of the CRIPS study. The rest of the scale was included in the data analysis in this thesis. The reliability and convergent validity of part one have been confirmed when compared to other validated scales for each symptom (Gallagher et al., 2012). Part, I, covers non-motor symptoms, including hallucination and psychosis, depression, anxiety, apathy, features of

DDS, sleep problems, daytime sleepiness, pain and other sensations, urinary problems, constipation problems, lightheadedness on standing, and fatigue. Part II has also been reported to have construct validity as subscale (Forjaz & Martinez-Martin, 2006). Part II covers speech, saliva and drooling, chewing and swallowing, eating tasks, dressing, hygiene, handwriting, hobbies and other activities, turning in bed, tremors, getting out of bed, a car, or a deep chair, walking and balance, and freezing. Several items in Part I and Part II, such as DDS (Evans et al., 2004), tremors (Achey et al., 2018), psychiatric symptoms (Keitel et al., 2013), and pain and sensations (Cury et al., 2014), are reported to have various relationships with mood, apathy, and other outcomes of interest the CRISP study. Therefore, they are utilised in the data analysis in this thesis. The self-rated parts took participants less than 10 minutes to complete (Part Ib and Part II).

Strength: Reliability, Validity, and widely used.

Weakness: It takes 10 minutes to complete.

11- **Work and Social Adjustment Scale (WSAS):** This self-report scale measures impairment in functioning (Mundt et al., 2002). Impaired work and social life by PD can be measured using the WSAS due to its simplicity, reliability, and validity. The WSAS has been shown to have good reliability and validity in a large cohort of patients with anxiety and depression (Zahra et al., 2014). It is sensitive to changes over time after treatment among patients with mood disorder and phobic disorder (Mataix-Cols, 2005; Zahra et al., 2014). The scale is also reported to be reliable to use in studies investigating impulsive behaviours in PD (Okai et al., 2013c). The WSAS can be an additional outcome measure because it measures work and social functioning factors.

Furthermore, a score on WSAS that exceeds 20 indicates moderately severe or worse functioning impairment. Significant functional impairment is also found in scores between 10 and 20, but clinical symptoms are less severe. Subclinical populations appear to have scores below 10 (Mataix-Cols, 2005; Zahra et al., 2014). Based on this information, a score above 15 is a cutoff point for clinically significant impairment in social and life adjustment. Furthermore, there is a separate question related to participants' employment status on the scale. The CRISP study analysed the impulsivity differences between retired and non-retired participants. Due to an error in the questionnaire preparation, the questionnaires asked participants whether their lives and work have been impacted by impulsive behaviours instead of PD. In some instances, the error was fixed, but in others, the

information remained unchanged in the database. This provided an opportunity to test if the PICS correlates with the total score of WSAS among those who completed the 'mistyped' version. This was because the PICS covers the social effects of Impulsive Behaviours.

Strength: Easy, simple, and reliable in other psychiatric disorders

Weakness: Limited data/use in PD cohorts.

12- **Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behaviour Scale (UPPS-P)**: The UPPS-P Impulsive Behaviour Scale is a revised version of the original UPPS (Whiteside & Lynam, 2001) and contains 59 items (Cyders et al., 2007). Four impulsive personality traits are reflected on the self-reported, multifaceted, and multidimensional scale: (i) Negative urgency, having a tendency to act rashly when experiencing extreme negative emotions; (ii) Lack of Premeditation: the habit of acting without thinking; (iii) Lack of Perseverance: not being able to remain focused on a task and (iv) Sensation Seeking: tending to seek out new exciting experiences. In 2007, the scale's authors noted that their model measures impulsive behaviours under intense negative emotions but does not cover the impulsive behaviours under intense positive emotions, which the literature did not adequately conceptualise or measure. As a result, the authors designed a scale for positive urgency, which was later included in the UPPS-P scale. Positive urgency is a tendency to act rashly when feeling great positive emotions (Cyders et al., 2007). The concept of impulsivity is multidimensional and plays a significant role in understanding various psychopathological problematic behaviours.

For this reason, it is frequently mentioned as a criterion for multiple disorders in the fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (e.g., Substance Use Disorders, Bipolar Disorder, Antisocial Personality Disorder, Conduct Disorder, Attention Deficit Hyperactivity Disorder, Borderline Personality Disorder). The search for understanding the relationship between personality traits and impulsivity is an ongoing mission with inconsistent findings. Most of these studies use the Big Five personality model (extraversion, openness, agreeableness, neuroticism, and conscientiousness) (Hair & Hampson, 2006; Lange et al., 2017). Due to these inconsistencies, researchers are now investigating other, perhaps, mediating factors that can cause problematic behaviours such as ICBs. One factor introduced is self-control, which enables individuals to keep impulses

in line with a healthy functioning level and has shown a negative correlation with impulsivity (Mao et al., 2018).

That said, the general understanding is that all these distinct constructs of personality traits relate to distinct aspects of impulsivity. Impulsiveness, sensation seeking, and control were all included in earlier models as components of personality traits (Whiteside & Lynam, 2001). The UPPS-P measures all known personality traits that are crucial to impulsivity. The original version (Giovannelli et al., 2023), the revised version of the scale (Bayard et al., 2016; Boussac et al., 2022) and the shorter version (Marques et al., 2022) have all been shown to be valid in PD studies. The original version of the scale has also been used to monitor personality before and after STN-DBS (Pham et al., 2015). In addition, the translated UPPS-P Impulsive Behaviour Scale has also been shown to maintain good psychometric properties across different cultures (Pinto et al., 2021). However, the complexity of personality, especially impulsivity, makes it unsafe to rely on such scales, as patients may soften their impulsivity-related ratings for various reasons. Nevertheless, while QUIP-RS and PICS assessed for the presence and the severity of impulsive behaviours, the UPPS-P was added to attempt to elucidate the relationship of the personality traits with ICBs and the impact of STN-DBS on each.

Strength: It has good validity overall, focusing on impulsivity-related personality traits.

Weakness: There is a lack of information regarding the scale's sensitivity to change and psychometric properties in STN-DBS cohorts. The scale takes more than 10 minutes to complete.

3.3.12.2 Other Materials

In addition to all rating scales, this subsection provides information on materials utilised in gathering information. All questionnaires were mailed to participants via 1st class Royal Mail service. In the mail, in addition to the questionnaires for each time point, participants were provided with a prepaid 1st class envelope to mail back once they completed them. Participants could ask for the questionnaires to be emailed or read over the phone. During the data collection period for each time point, participants were contacted to schedule an over-telephone interview and follow up on the status of their self-rated questionnaires. Over the telephone, some participants did not sound clear due to PD effects on their speech. Therefore, a mobile app called Rogervoice (android) was used in such cases. The Rogervoice app provided a live

transcription of participants' answers to facilitate understanding. The app did not allow recording of the voice or the transcript as data and privacy policies were considered. Patients were made aware of the process.

3.4 Results

The statistical data analysis results from the CRISP study are presented in this chapter. Subsequently, the results of the retrospective review are presented.

3.4.1 Prospective Multicentre Observational Study – CRISP Study

Table 18 displays the number of recruited participants (n=73) from each participating centre. In the CRISP study's original database, there are 4 cases of GPi-DBS, whereas other participants received STN-DBS. Due to their small number, the GPi-DBS cases were not used for data analysis in this thesis. Of all the potential participants contacted, 5/80 rejected joining the study for undisclosed reasons, and 2/80 informed us that they had refused the DBS operation for undisclosed reasons. Therefore, 73 patients have been recruited up to date. The DBS implantation caused an infection in 1/73 of the participants, resulting in device removal. However, the demographics and T0 data for the participants were utilised for descriptive analysis at T0. Of all the participants that have been recruited, 1 patient passed away after completing the T2 due to haemorrhagic stroke. Per their preferences, the self-rated questionnaires were read over the phone for 4/73 participants, and only 2 required this method for every time point. Lastly, the Rogervoice app was required only for 5/73 patients.

The following subsection provides a descriptive statistical analysis for all recruited participants who completed self-rated and RF-completed questionnaires. The outcomes for the total 73 participants are analysed as a case series.

Table 18 Number of Participants from Each Participating DBS Centre.

Participating DBS centre	Number of recruited participants
London	13
Liverpool	9
Oxford	13
Romford	3
Salford	14
Glasgow	14
Newcastle	7
Total	**73**

Summary Points: Descriptive Statistics at Baseline

- 69% (n=50) of the participants identified themselves as male,
- 96% (N=70) identified as White British for ethnicity.
- The carers of 58 out of 73 participants consented to join the study

3.4.2 Descriptive Statistical Analysis at Baseline

Table 19 displays the demographic characteristics of participants at each follow-up. About 69% (n=50) of the participants identified themselves as male, and 96% (N=70) identified as White British for ethnicity. Ethnicities will not undergo any further analysis due to the underrepresentation of other ethnicities. About 80% (n=58) of recruitment was completed before the DBS operation, and the remaining 20% (n=15) were recruited after the operation (before activation of the DBS device). The carers of 58 out of 73 participants consented to join the study with their patient/relative/client. The relationship between patients and carers was not specified. The remaining 15 out of 73 participants did not have a carer available or declined to participate in the study. For carers, demographics and other potentially relevant information were not gathered.

The frequency of all Parkinson's and related medications at all follow-ups (T0 and T2) is displayed in *Table 21*. Participants may have used medication that does not relate to PD, such as benign prostatic hyperplasia or hypertension. Those medications were not included in our data gathering. At T0, the most frequently used antiparkinsonian medication along with Levodopa was Dopamine Agonists (DA) at 53% (n=39), followed by Type-B Monoamine Oxidase Inhibitors (MOA-B) at 49%(n=35), Catechol-O-methyl transferase Inhibitors (COMT Inhibitors) at 23% (n=17), amantadine at 26% (n=19), and anticholinergics at 3% (n=2), , and, respectively. As shown in *Table 20*, 18% (n=13) of participants were on Levodopa therapy alone. The percentage of participants in 2, 3, 4 and 5 classes of PD medications was 26% (n=19), 42% (n=30), 11% (n=8), and 3% (n=2), respectively. Therefore, being prescribed 3 different classes of PD medication was the most common combination at 42%. The result for their frequency and the frequency of participants on more than 3 classes of PD medication is shown in *Table 20*.

Table 19 Demographic Characteristics for Each Time Point

	T0 (Baseline)	**T2 (6-month follow-up)**
N=	73	61
Age at operation Mean (std. Deviation)	62 (7)	62 (7)
Age at diagnosis Mean (std. Deviation)	51 (8)	52 (8)
Disease duration Mean (std. Deviation)	10 (4)	10 (4)
Retired/not working (%)	44 (60%)	34 (55%)
Gender		
♂ *(%)*	50 (69%)	44 (72%)
♀ *(%)*	23 (31%)	17 (28%)
Ethnicity		
White British (%)	70 (96%)	59 (97%)
Others (%) ⟷	3 (4%)	2 (3%)
Recruitment time		
Before operation (%)	58 (80%)	48 (79%)
After operation (%) ∇	15 (20%)	13 (21%)
Carers N=	58	44

⟷*Other ethnicities included 1 Arab, 1 Indian British, and 1 white Romanian (1 white Romanian missed T2).*

∇ *For "after operation" recruitments", their data collection was completed before DBS activation.*

Table 20 Frequency of Cases of Multiple Antiparkinsonian Medications (Rounded %)

	1 PD Rx class*	2 PD Rx class	3 PD Rx class	4 PD Rx class	5 PD Rx class	Multi-PD Medication	
						≤2	≥3
T0 (N=73)	18%	26%	42%	11%	3%	44%	56%
T2 (N = 61)	29%	29%	34%	7%	0%	41%	50%

PD Rx = Parkinsonian medication classes, including Levodopa.

**Participants on only Levodopa*

Note: No participant was on all 6 classes of medications listed in Table 21.

The results for descriptive statistics for all scales and main outcomes at the baseline (T0) and 6-month follow-up (T2) are presented in *Table* 26.

All data was collected at the baseline for 73 participants, except for the work and social adjustment scale (WSAS), which was available for only 41 participants due to an error in preparing mails. In the following subsection, the result of descriptive statistical analysis for impulsive control disorders (ICDs) and other related impulsive compulsive behaviours (ICBs) are presented in more detail.

Table 21 Frequency of Antiparkinsonian and Other Medications by Their Class

Antiparkinsonian agents	**T0 (Rounded %)**	**T2 (Rounded %)**
Levodopa Use frequency §	100%	100%
DA Use frequency §§	53%	46%
*MAOB Use frequency**	49%	38%
*COMT inhibitors use frequency***	23%	18%
Amantadine Use frequency	26%	16.4%
*Anticholinergics Use frequency ****	3%	1.6%
Psychotropics Use frequency ∇	31%	43%
*Pain Killers *****	12%	10%
Sleep Medications§§§	12%	13%

DA=Dopamine Agonists, COMB inhibitors=Catechol-O-methyl transferase Inhibitors, MOAB= Type-B Monoamine Oxidase Inhibitors

∇ Psychotropic use can be used for distinct or comorbid psychiatric disorders. Including: Melatonin, Citalopram, Escitalopram, Quetiapine, Mirtazapine, Clonazepam, Temazepam, Sertraline, Amitriptyline

§ In the CRISP cohort, this includes Madopar, Madopar controlled release, Sinemet, Sinemet Control Released, Staleveo

§§ In the CRISP cohort, this includes Pramipexole, Ropinirole, Rotigotine

** In the CRISP cohort, this includes Selegiline, rasagiline, and safinamide*

*** In the CRISP cohort, this includes Entacapone, Opicapone*

**** In the CRISP cohort, this includes Artane (Trihexyphenidyl)*

***** In the CRISP cohort, this includes Orphenadrine, Pregabalin, Co-codamol, Gabapentin, Duloxetine (prescribed mainly for pain)*

§§§ In the CRISP cohort, this includes Melatonin, Clonazepam, Temazepam

Table 22 Results for All Outcomes at T0 and T2

	T0 (N=73)		(T2) (N=61)	
	Mean	***SD***	***Mean***	***SD***
*Total LEDD **	1182	*591*	764	375.4
*QUIP-RS ICDs total ***	8.1	8.6	6.7	7.3
Hobbysm-Punding	5.5	5.8	3.7	4.5
DDS	2	3	1.4	2.3
PICS	1.5	3.4	1.2	2.1
GAD-7	5.5	4.5	3.5	3.8
NPI-12	*13.3*	11.7	9.9	11
Psychosis (Items 1 &2)	*.2*	*1*	.02	.1
PHQ-9	8.5	5.2	7.8	5.2
Suicidality	1.8	.5	.21	.5
PDQ-39	53.3	23.67	43.3	22
Stigma	5.5	4	4.3	3.6
Emotional Well being	8.2	4	7.4	5
Cognition	5	3	4	3
*WSAS (n=41) ****	20.9	9.6	16.6	9.4
EQ-5D-5L VAS	59.23	18.1	63	15
AES	51.7	7.6	52	8
SHAPS	1.3	*1.8*	1.1	1.5
MDS-UPDRS Part I	15.1	6.2	14	6.1
Part II	19.4	7.8	15.7	6.6
Part IV	11.22	3.9	6.5	4.6

	T0 (N=73)		(T2) (N=61)	
	Mean	***SD***	***Mean***	***SD***
Total Sleep Hours	6.8	1.7	7.5	1.5
UPPS_P	117.3	20	160	16
UPP	69	14	104	12
Negative Urgency	23.7	5.6	35	5.8
Lack of Premeditation	20.9	5.1	22	5.5
Lack of Perseverance	20.9	5	23	3.6
Sensation seeking	28.19	6.8	33	6.7
Positive Urgency	*23.5*	7.3	45.7	7.3
ZBI- Carers	14.7	15.6	11.7	8.7

LEDD = Levodopa Equivalent Daily Dose, QUIP-RS= the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, DDS= Dopamine Dysregulation Syndrome ICDs= Impulsive Control Disorders, PICS= The Parkinson's Impulse-Control Scale, GAD-7=General anxiety Disorder_7 items, NPI-12=Neuropsychiatric Inventory-12 Item, PHQ-9= Patient Health Questionnaires, PDQ-39=Parkinson's disease Questionnaires-39 Items, WSAS=Work and Social Adjustment Scale, EQ-5D-5L= European Quality of life-5 Dimension-5 Levels, AES=Apathy Evaluation Scale, SHAPS= Smith-Hamilton Pleasure Scale, MDS-UPDRS=The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale, UPPS-P = the Urgency (lack of)-Premeditation (lack of)-Perseverance (lack of)-Sensation Seeking-Positive Urgency(lack of), UPP= the Urgency (lack of), Perseverance (lack of) and Positive Urgency(lack of), ZBI=Zarit Burden Interview, EQ-VAS= European Quality-Visual Analog Scale, IQR= Interquartile (25th and 75th, In case, 25th quartile was 0, the middle quartile is reported)

**Total LEDD was calculated using https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm*

*** ICDs are compulsive gambling, binge eating, hypersexuality, and compulsive shopping.*

****Due to an error in preparing mails, the WSAS was only available for 41 participants.*

Summary Points: Frequency of Positive Cases of ICBs in Pre-defined Groups at Baseline

- The frequency of cases scored above the cutoff point (>10) on the QUIP-RS was 26% (n=19).
- The difference of the ICDs total and gambling was negligible between the DA Use subgroups.
- Male participants had a higher frequency of positive cases of the ICDs total
- The frequency for the ICDs total score and other ICBs was higher in the late-onset subgroup.
- The frequency of hobbyism-punding was exceptionally higher in the working subgroup.
- The users of psychotropics had a higher frequency of positive cases of the ICDs total and all other ICBs except for gambling and hypersexuality.
- The frequency of positive cases for most ICBs and the ICDs total was higher in the clinically significant anxiety subgroup, the depression subgroup, and apathy.

3.4.3 Frequency of Positive Cases of ICBs in Pre-defined Groups at Baseline

Table 25 and *26* present the frequency of positive cases (above the cutoff point) on the QUIP-RS and the PICS and the difference in gender, PD onset, median LEDD, unemployment, Dopamine Agonist (DA) Use, and Psychotropic Use groups at T0. *Table 27* presents the same differences in the groups that were created based on scoring above a cutoff point on corresponding scales for clinically significant depression, anxiety, and apathy. Of note, although in the result tables, the frequency difference of positive cases of ICBs (binary variable) is shown in various groups, the Mann-Whitney *U* test examines the difference of the total score of individual ICBs and ICDs total (continuous variable) on the QUIP-RS and PICS in all groups. The effect size for statistically significant results was calculated using the following equation, $r^2 = z^2/n - 1$ in Excel. As 4 tests are conducted for ICDs, the tests are done for the other related ICBs, and the corrected α level was calculated by dividing .05 by 4.

However, the α level remained at .05 for the ICDs total, hobbyism-punding, and DDS. The following is the result of an analysis of impulsive behaviour on the QUIP-RS.

At T0, the frequency of cases in which the total score reached above the cutoff point (>10) on the QUIP-RS was 26% (n=19). Male participants had a higher frequency of positive cases of the ICDs total (n=23, 32%) than their female counterparts (n=23, 13%). The trend was similar for the frequency of all individual ICBs on the QUIP-RS, except for compulsive shopping, which was higher among female participants (n=6, 8.7%) than male participants (n=2, 2%). However, only the total score of hypersexuality was found to be significantly different across the two genders. Lastly, there were no positive cases of compulsive gambling and hypersexuality among female participants at the T0.

The frequency of positive cases of ICBs was also different across early-onset and late-onset subgroups. The frequency for the ICDs total score (n=7, 18.4% *vs* n=12, 34%) and other ICBs was higher in the late-onset subgroup (n=35). The compulsive shopping positive cases were exceptionally more common in the early-onset subgroup (5.3% vs 2.9%). Nevertheless, only the difference in the total score of binge eating was statistically significant across the subgroups. Next, the relationship between total LEDD as a severity indication of PD motor symptoms with ICB scores was investigated. Except for the DDS, which was higher in the above-median subgroup (19.4% vs 13.5%), the frequency of all other ICBs, in addition to the ICDs total, was more common in the below-median subgroup. However, their total scores were not statistically significant across the subgroups. Of note, in the above median subgroup, compulsive gambling, hypersexuality, and compulsive shopping had 0 positive cases.

Of 73 participants, 44 were reported to be retired/not working. The frequency of impulsivity was higher in the retired/notworking subgroup for the ICDs total, compulsive gambling, binge eating, compulsive shopping and DDS. The frequency of hobbyism-punding was exceptionally higher in the working subgroup (41% vs 27.3%). The difference in total scores between the two subgroups was insignificant for any of the above.

The frequency difference of positive cases of the ICDs total and compulsive gambling was negligible between the DA Use subgroups. Furthermore, although the difference was noteworthy for hypersexuality, compulsive shopping and other related ICBS for the frequency of positive cases, their total score did not significantly differ across the subgroups. In the next step, the relationship between being prescribed psychotropic agents and impulsive behaviours

was tested. The users of psychotropics had a higher frequency of positive cases of the ICDs total, and all other ICBs except for compulsive gambling and hypersexuality, which had a higher frequency in the other subgroup, at 4.3% vs 6% and 4.3% vs 8%, respectively. However, the difference in the total score for ICDs total reached a significant level, while that for hobbyism-punding was nearly significant.

The analysis of the link between ICBs and psychiatric comorbidities was broadened by testing the difference in impulsivity scores across three psychiatric comorbidities. The frequency of positive cases for all ICBs and the ICDs total was higher in the clinically significant anxiety subgroup (GAD-7, cutoff=10). However, the total score was only significant for the ICDs total, hobbyism-punding and DDS. As for the clinically significant depression subgroup (PHQ-9, cutoff=9), except for compulsive gambling, the frequency of positive cases of ICBs and the ICDs total and their total score was significantly higher in the clinically significant depression subgroup. As for the participants with clinically significant apathy (AES, cutoff point=38), the frequency of positive cases of ICDs total and all individual ICBs was higher. However, only the total score of the ICDs total, compulsive gambling, hypersexuality and DDS reached a significant level. The correlation between the ICDs total on the two impulsivity scales with other main outcomes listed in *Table 28* was further analysed. The ICDs total showed a significant weak correlation with age at operation, the pleasure scale (SHAPS), UPDRS, I and II. It showed a similar correlation with the UPPS-P total score, negative and positive urgency. However, the negative urgency trait showed a significant moderate positive correlation with the ICDs' total score.

To find which ICBs are correlated to each other, a Spearman correlation test was conducted for all ICBs on the QUIP-RS. As shown in *Table 23*, compulsive shopping showed a significant moderate correlation with hobbyism-punding. Hypersexuality and compulsive gambling showed a significant weak positive correlation with DDS and binge eating, respectively. Among all ICBs, only binge eating and hobbyism-punding showed a significant weak positive correlation with more than one ICB.

Table 23 Correlation Between Individual ICBs Measured on QUIP-RS

	C. Gambling	**Hypersexuality**	**Binge eating**	**C. Shopping**	**Hobbysm-punding**
	Spearman correlation coefficient *r, *p* value**				
Compulsive Gambling	-	-.062, p = .6	-	-	-
Hypersexuality	-.062, p = .6	-	-	-	-
Binge eating	**.323, p = .005**	.075, p =.5	-	-	-
Compulsive shopping	-.050, p = .6	-.035, p = .7	.158, p = .1	-	-
Hobbysm + punding	.084, p = .4	-.062, p = .6	**.232, p = .049**	**.569, p < .001**	-
DDS	-.050, p = .6	**.388, p<.001**	.080, p = .5	-.028, p = .8	-.050, p = .6

**The power for Spearman's correlation was calculated on SPSS for a small effect size (.3) =.71. The*

Lastly, the frequency of cases with multiple positive ICDs is shown in *Table 24*. The frequency of multiple ICDs was 9.6%, with cases of two ICDs being the most common at 6.8%.

Table 24 Frequency of Cases with Multiple ICDs at T0 And T2

	T0	T2
No. of ICDs	Frequency (%)	
2	5 (6.8%)	2 (3.3%)
3	1 (1.4%)	0
4	1 (1.4%)	0
Total	7 (9.6%)	2 (3.3%)

Table 25 The Frequency of Positive Impulsivity in Gender, PD Onset and LEDD Median Groups

	scales	Total (N=73)	Gender			PD onset			LEDD Median		
			♂ (n=50)	♀ (n=23)	Difference (Mann-Whitney *U*)	Early-onset <50 (n=38)	Late-onset >50 (n=35)	Difference (Mann-Whitney *U*)	Below Median <1103 (n=37)	Above median >1103 (n=36)	Difference (Mann-Whitney *U*)
			Corrected α level: ICDs = .0125, ICDs totals and Other related ICBs: .05								
ICDs	QUIP-RS	26%	32%	13%	*U*= 432, *p* = .08	18.4%	34.3%	***U*= 891, *p* = .01** ***Effect size*: .08**	27%	25%	*U*= 649, *p* = .8
	PICS	12.3%	12%	13%	*U*= 589 *p* = .8	10.5%	14.3%	*U*= 749, *p* = .2	13.5	11%	*U*=688, *p* = .7
Gambling	QUIP-RS	5.5%	8%	0%	*U*= 552 *p* = .3	5.3%	5.7%	*U*= 628, *p* = .5	10%	0%	*U*= 601, *p* = .2
	PICS	1.4%	2%	0%	*U*= 542 *p* = .4	2.6%	0%	*U*= 669, *p* = .9	2.7%	0%	*U*=628, *p* = .3
Hypersexuality	QUIP-RS	6.8%	10%	0%	***U*= 295 *p*<.001** ***Effect size*: .16**	5.3%	8.6%	*U*= 745, *p* = .3	8.1%	5.6%	*U*=713, *p* = .5
	PICS	4.1%	6%	0%	*U*= 540 *p* = .2	2.6%	5.7%	*U*= 684, *p* = .5	2.7%	5%	*U*=685, *p* = .5
	QUIP-RS	17.8%	18%	17.4%	*U*= 463 *p* = .1	10.5%	25.7%	***U*= 962, *p* < .001**	21.6%	13.9%	*U*=643, *p* = .7

	scales	Total (N=73)	Gender			PD onset			LEDD Median		
			♂ (n=50)	♀ (n=23)	Difference (Mann-Whitney *U*)	Early-onset <50 (n=38)	Late-onset >50 (n=35)	Difference (Mann-Whitney *U*)	Below Median <1103 (n=37)	Above median >1103 (n=36)	Difference (Mann-Whitney *U*)
			Corrected α level: ICDs = .0125, ICDs totals and Other related ICBs: .05								
								***Effect size*: .15**			
Binge Eating	PICS	9.6%	8%	13%	*U*= 625 *p* = .39	7.9%	11.4%	*U*= 723, *p* = .3	10%	8.3%	*U*=645, *p* = .7
	QUIP-RS	4.1%	2%	8.7%	*U*= 626 *p* = .5	5.3%	2.9%	*U*= 737, *p* = .3	8.1%	0%	*U*=688, *p* = .7
Compulsive Shopping	PICS	0%	-	-	-	-	-	-	-	-	-
	QUIP-RS	32%	36%	26%	*U*= 491 *p* = .3	26%	40%	*U*= 771, *p* = .2	35%	3.6%	*U*=666, *p* = .9
Hobbysm+Punding	PICS	4.1%	0%	13%	*U*= 620 *p* = .2	5.3%	2.9%	*U*= 704, *p* = .3	5.4%	2.8%	*U*=665, *p* = .9
	QUIP-RS	16.4%	20%	8.7%	*U*= 480 *p* = .2	15.8%	17.1%	*U*= 744, *p* = .3	13.5%	19.4%	*U*=765, *p* = .2
DDS	PICS	0%	-	-	-	-	-	-	-	-	-

LEDD = Levodopa Equivalent Daily Dose, QUIP-RS= the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, DDS= Dopamine Dysregulation Syndrome ICDs= Impulsive Control Disorders, PICS= The Parkinson's Impulse-Control Scale. The effect size for the statistically significant result was calculated using the following equation ($r^2 = z^2/n - 1$) in Excel. Z stands for the standardised test statistic. For compulsive gambling, hypersexuality, binge eating and compulsive shopping, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/4) =.0125

Table 26 The Frequency of Positive Impulsivity in Working Status, DA Use and Psychotropic Use Groups

	scales	Total (N=73)	Working Status (Retired?)			DA Use			Psychotropics user		
			Yes (n=44)	No (n=29)	Difference (Mann-Whitney *U*)	Yes (n=39)	No (n=34)	Difference (Mann-Whitney *U*)	Yes (n=50)	No (n=23)	Difference (Mann-Whitney *U*)
		Corrected α level: ICDs =.0125, ICDs totals and Other related ICBs: .05									
*ICDs **	**QUIP-RS**	26%	27%	24%	*U*= 628, *p* = .9	25.6%	26.5%	*U*= 568, *p* = .2	34.8%	22%	*U*= 675, *p* = .2
	PICS	12.3%	9.1%	17.2%	*U*= 558, *p* = .2	10.3%	14.7%	*U*= 657, *p* = .9	21.7%	8%	***U*= 710, *p* = .04** ***Effect size*: .05**
Gambling	**QUIP-RS**	5.5%	6.8%	3.4%	*U*= 685, *p* = .4	5.1%	5.9%	*U*= 558, *p* = .08	4.3%	6%	*U*= 639, *p* = .2
	PICS	1.4%	2.3%	0%	*U*= 652, *p* = .7	0%	2.9%	*U*= 616, *p* = .2	4.3%	0%	*U*= 579, *p* = .9
Hypersexuality	**QUIP-RS**	6.8%	6.8%	6.9%	*U*= 606, *p* = .7	5.1%	8.8%	*U*= 583, *p* = .3	4.3%	8%	*U*= 609, *p* = .6
	PICS	4.1%	0%	10.3%	*U*= 572, *p* = .03	5.1%	2.9%	*U*= 678, *p* = .6	4.3%	4%	*U*= 578, *p* = .9
Binge Eating	**QUIP-RS**	17.8%	20%	13.8%	*U*= 597, *p* = .6	5.1%	2.9%	*U*= 569, *p* = .2	21.7%	16%	*U*= 683, *p* = .1
	PICS	9.6%	9%	10%	*U*= 642, *p* = .7	7.7%	11.8%	*U*= 655, *p* = .9	17.4%	6%	*U*= 672, *p* = .1

	scales	Total (N=73)	Working Status (Retired?)			DA Use			Psychotropics user		
			Yes (n=44)	No (n=29)	Difference (Mann-Whitney *U*)	Yes (n=39)	No (n=34)	Difference (Mann-Whitney *U*)	Yes (n=50)	No (n=23)	Difference (Mann-Whitney *U*)
			Corrected α level: ICDs =.0125, ICDs totals and Other related ICBs: .05								
Compulsive Shopping	**QUIP-RS**	4.1%	4.5%	3.4%	*U*= 738, *p* = .2	5.1%	2.9%	*U*= 720, *p* = .5	8.7%	2%	*U*= 680, *p* = .07
	PICS	0%	-	-	-	-	-	-	-	-	-
Hobbysm+Punding	**QUIP-RS**	32%	27.3%	41.4%	*U*= 626, *p* = .8	28.2%	38.2%	*U*= 598, *p* = .4	43.5%	28%	*U*= 719, *p* = .08
	PICS	4.1%	6%	0%	*U*= 620, *p* = .6	5.1%	2.9%	*U*= 656, *p* = .8	8.7%	2%	*U*= 652, *p* = .053
DDS	**QUIP-RS**	16.4%	18.2%	13.8%	*U*= 677, *p* = .6	12.8%	20.6%	*U*= 589, *p* = .3	21.7%	14%	*U*= 619, *p* = .5
	PICS	0%	-	-	-	-	-	-	-	-	-

LEDD = Levodopa Equivalent Daily Dose, QUIP-RS= the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, DDS= Dopamine Dysregulation Syndrome ICDs= Impulsive Control Disorders, PICS= The Parkinson's Impulse-Control Scale, the Effect size for the statistically significant result was calculated using following equation ($r^2 = z^2/n - 1$) in Excel. The Z stands for standardised test statistic. For compulsive gambling, hypersexuality, binge eating and compulsive shopping, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/4) =.0125

Table 27 The Frequency of Cases of Positive Impulsivity in Clinically Significant Anxiety, Depression and Apathy Groups

	scale	Total	Anxiety (GAD-7, cutoff=10)			Depression (PHQ-9, cutoff=9)			Apathy (AES, cutoff=38)		
		Total (N=73)	**>10 (n=12)**	**<10 (n=61)**	**Difference (Mann-Whitney *U*)**	**>9 (n=39)**	**<9 (n=34)**	**Difference (Mann-Whitney *U*)**	**> 38 (n=21)**	**<38 (n=52)**	**Difference (Mann-Whitney *U*)**
		Corrected α level: ICDs =.0125, ICDs totals and Other related ICBs: .05									
*ICDs **	QUIP-RS	26%	58%	19.7%	***U*= 534, *p* = .01** ***Effect size*: .08**	43.6%	5.9%	***U*= 1093, *p* = .001** ***Effect size*: .3**	47%	17%	***U*= 711, *p* = .008** ***Effect size*: .09**
	PICS	12.3%	41%	6.6%	***U*= 518, *p* = .005** ***Effect size*: .1**	15.4%	8.8%	*U*= 706, *p* = .3	13.5%	9.5%	*U*= 524, *p* = .6
Gambling	QUIP-RS	5.5%	8.3%	4.9%	*U*= 424, *p* = .1	10.3%	0%	*U*= 778, *p* = .056	19%	0%	***U*= 650, *p* = .001** ***Effect size*: .14**
	PICS	1.4%	8.3%	0%	*U*= 369, *p* = .9	2.6%	0%	*U*= 680, *p* = .3	4.8%	0%	*U*= 572, *p* = .1
Hypersexuality	QUIP-RS	6.8%	8.3%	6.6%	*U*= 464, *p* = .1	12.8%	0%	***U*= 911, *p* = .005** ***Effect size*: .1**	19%	1.9%	***U*= 639, *p* = .009** ***Effect size*: .09**
	PICS	4.1%	16.7%	1.6%	*U*= 421, *p* = .016	2.6%	5.9%	*U*= 641, *p* = .4	4.8%	3.8%	*U*= 551, *p* = .8
	QUIP-RS	17.8%	33.3%	14.8%	***U*= 523, *p* = .01**	28.2%	5.9%	***U*= 1035, *p* = .001**	28.6%	13%	*U*= 628, *p* = .1

	scale	Total	Anxiety (GAD-7, cutoff=10)			Depression (PHQ-9, cutoff=9)			Apathy (AES, cutoff=38)		
		Total (N=73)	>10 (n=12)	<10 (n=61)	Difference (Mann-Whitney *U*)	>9 (n=39)	<9 (n=34)	Difference (Mann-Whitney *U*)	> 38 (n=21)	<38 (n=52)	Difference (Mann-Whitney *U*)
		Corrected α level: ICDs =.0125, ICDs totals and Other related ICBs: .05									
Binge Eating					***Effect size*: .08**			***Effect size*: .2**			
	PICS	9.6%	33%	4.9%	*U*= 477, *p* = .019	12.8%	5.9%	*U*= 709, *p* = .3	19%	5.8%	*U*= 618, *p* = .08
	QUIP-RS	4.1%	16.3%	1.3%	*U*= 501, *p* = .03	7.7%	0%	***U*= 1024, *p* = .001**	9.5%	1.9%	*U*= 587, *p* = .1
Compulsive Shopping								***Effect size*: .2**			
	PICS	0%	-	-	***U*= 427, *p* = .001**	-	-	*U*= 663, *p* = 1	-	-	*U*= 546, *p* = 1
					***Effect size*: .24**						
	QUIP-RS	32%	75%	24.6%	***U*= 518, *p* = .02**	53%	8.8%	***U*= 1026, *p* = .001**	47%	26.9%	*U*= 659, *p* = .09
Hobbysm+Punding					***Effect size*: .22**			***Effect size*: .2**			
	PICS	4.1%	3.3%	8.3%	*U*= 404, *p* = .2	5.1%	2.9%	*U*= 667, *p* = .6	0%	5.8%	*U*= 514, *p* = .2
	QUIP-RS	16.4%	50%	9%	***U*= 514, *p* = .01**	30.8%	0%	***U*= 963, *p* = .001**	38.1%	7.7%	***U*= 712, *p* = .002**
DDS					***Effect size*: .06**			***Effect size: .2***			***Effect size*: .1**
	PICS	0%	-	-	*U*= 354, *p* = .5	-	-	*U*= 663, *p* = 1	-	-	*U*= 546, *p* = 1

*LEDD = Levodopa Equivalent Daily Dose, QUIP-RS= the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, DDS= Dopamine Dysregulation Syndrome ICDs= Impulsive Control Disorders, PICS= The Parkinson's Impulse-Control Scale, GAD-7=General anxiety Disorder_7 items, PHQ-9= Patient Health Questionnaires, AES=Apathy Evaluation Scale. The effect size for the statistically significant result was calculated using the following equation ($r^2 = z^2/n - 1$) in Excel. Z stands for standardised test statistic. * For compulsive gambling, hypersexuality, binge eating and compulsive shopping, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/4) =.0125*

3.4.4 Correlation of Impulsivity with Other Outcomes of Interest at Baseline

A correlation analysis was conducted using Spearman's correlation to understand further the relationship between baseline impulsivity and other main outcomes, including age at operation and total LEDD. The power calculation on the SPSS software was conducted for Spearman's correlation at .71. The results of the ICDs total correlation on the QUIP-RS are presented in this section. The ICDs total score showed a weak positive correlation with age at the operation, the pleasure scale (SHAPS), the non-motor experience of living with PD (UPDRS, I), the depression scores on the same part of the UPDRS, activities of daily living (UPDRS, II) *Table 28*. Regarding the quality of life, the PDQ-39 showed a trend of weak positive correlation. Of note, the correlation was non-significant with the NPI-12 despite showing a significant difference in clinically significant depression and anxiety, as presented in *Table 27*. The same analysis was carried out for other related ICBs (hobbyism-punding and DDS) on both scales (QUIP-RS and PICS). Hobbyism-punding total score on the QUIP-RS showed a significant positive weak correlation with the PDQ-39 summary index (total score/8), as shown in *Table 29*. It also showed a trend of a negative, weak correlation with PD duration and UPDRS, IV. As for DDS (*Table 29)*, the positive weak correlation between the PDQ-39 summary index and its total score on the QUIP-RS showed a trend of significant level. It also showed a trend of significant positive weak correlation with part I and II. The correlation with the UPDRS, IV was negative for both hobbyist-pounding and DDS, but it is insignificant. As for the personality traits measured on the UPPS-P, the ICDs total showed a significant weak positive correlation with the UPPS-P total score. However, for the subscales, there was a significant weak positive correlation between negative and positive urgency and a significant moderate positive correlation with lack of perseverance. Of all traits measured on the UPPS-P, the ICDs total only showed a very weak negative correlation with sensation seeking, which was non-significant.

Table 28 Correlation of ICBs on QUIP-RS and PICs with Main Outcomes

	QUIP-RS ICDs total score		**PICS ICDs total score**	
	Spearman's correlation coefficient *r (73)* =	***p* value**	**Spearman's correlation coefficient *r (73)* =**	***p* value**
	Power for small effect size of .3 =.71. α level: .05			
Age-at-operation	**.242**	**.03**	.157	.1
PD Duration	-.056	.6	.127	.2
Total LEDD	-.079	.5	.105	.3
DA dosage	.055	.6	.021	.08
Sleep hours	.014	.9	.021	.8
Total PDQ-39	.218	.064	.162	.1
*Cognition**	**.446**	**<.001**	.204	.08
Total NPI-12	.183	.1	.162	.1
SHAPS	**.242**	**.03**	.067	.5
*UPDRS-I**	**.341**	**.003**	.313	.007
UPDRS-II	**.302**	**.01**	**.329**	**.004**
UPDRS-IV	-.047	.6	.079	.5
Total UPPS-P	**.256**	**.02**	.228	.05
*Negative Urgency**	**.386**	**.001**	**.346**	**.003**
Lack of premeditation	.036	.7	.056	.6
Lack of perseverance	**.441**	**.001**	.307	.008
Sensation seeking	-.142	.23	-.155	.1
Positive Urgency	**.274**	**.01**	**.289**	**.01**

LEDD = Levodopa Equivalent Daily Dose, QUIP-RS= the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, ICDs= Impulsive Control Disorders, PICS= The Parkinson's Impulse-Control Scale, NPI-12=Neuropsychiatric Inventory-12

*Item, PDQ-39=Parkinson's disease Questionnaires-39 Items, SHAPS= Smith-Hamilton Pleasure Scale, UPDRS= Unified Parkinson's Disease Rating Scale, UPPS-P = the Urgency (lack of)-Premeditation (lack of)-Perseverance (lack of)-Sensation Seeking-Positive Urgency(lack of). *For UPPS-P subscales, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/4) =.0125). For the UPDRS, I, II and IV, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/3) =.0116. For cognition, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/2) =.0.025*

Table 29 Correlation of Other Related ICBs with Age, PD Duration, NPI-12, PDQ-39, SHAPS and UPDRS, I, II, IV

	Hobbyism-Punding				**DDS**			
	QUIP-RS		**PICS**		**QUPI-RS**		**PICS**	
	Spearman's correlation *r (73) =*	***p* value**	**Spearman's correlation *r (73) =***	***p* value**	**Spearman's correlation *r (73) =***	***p* value**	**Spearman's correlation *r (73) =***	***p* value**
	Power for small effect size of .3 =.71. α level: .05 (ex. UPDRS part =.016*)							
Age at operation	.080	.5	.140	.2	.128	.2	.208	.07
PD duration	-.015	.9	.010	.9	.073	.5	-.059	.6
Sleep Hour	.006	.9	.186	.1	-.022	.1	-.116	.3
PDQ-39	**.283**	**.01**	.037	.7	.22	.057	.033	.7
NPI-12	.153	.1	.-.151	.2	.178	.1	.076	.5
SHAPS	.167	.1	.098	.4	.194	.1	-.161	.1
UPDRS, I	.181	.1	.079	.5	.197	.09	-0.18	.8
UPDRS, II	.169	.1	.205	.08	.199	.09	.09	.4
UPDRS, IV	-.038	.7	-.082	.4	-.002	.9	.050	.6

*QUIP-RS= the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, PICS= The Parkinson's Impulse-Control Scale, NPI-12=Neuropsychiatric Inventory-12 Item, PDQ-39=Parkinson's Disease Questionnaires-39 Items, SHAPS= Smith-Hamilton Pleasure Scale, UPDRS= Unified Parkinson's Disease Rating Scale, *For the UPDRS, I, II and IV, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/3) =.0116*

Summary Points: Correlation of Impulsivity with Personality Traits on the UPPS-P at Baseline

- The negative urgency was significantly correlated (positive) with compulsive gambling, hobbyism-punding and DDS.
- Lack of perseverance showed a weak positive correlation with hypersexuality and binge eating.
- The only personality traits that showed no significant correlation with either one of the ICBs were lack of premeditation and sensation seeking.

4.1.1 Correlation of Impulsivity with Personality Traits on the UPPS-P at Baseline

Additional analyses were conducted to understand the relationship between 5 personality traits measured on the UPPS-P with individual ICBs measured on the QUIP-RS. This part was not replicated for the results of the PICS. As shown in *Table 30*, only the negative urgency was significantly correlated with hobbyism-punding and DDS. It also showed a significant weak positive correlation with compulsive gambling. In addition, it showed a nearly significant weak positive correlation between hypersexuality and binge eating. Lack of perseverance showed a weak positive correlation with hypersexuality and binge eating. Of note, positive urgency showed a nearly significant weak positive correlation with hobbyism-punding and DDS. Therefore, the only personality traits that showed no significant correlation with either one of the ICBs were lack of premeditation and sensation seeking.

As a result, the relationship between the UPPS-P total and impulsivity was further investigated. A separate variable was created from the total score of the negative urgency, lack of perseverance, and positive urgency alone, excluding lack of premeditation and sensation seeking. The rationale for including the positive urgency is that positive urgency had a relatively stronger correlation with other ICBs than the other two traits. The new variable, the **U**rgency (lack of), **P**erseverance (lack of) and **P**ositive urgency (UPP), was utilised to determine if it remains correlated without the two omitted subscales (lack of premeditation and sensation seeking). As shown in *Table 31*, the UPP had a significant moderate correlation with the ICDs total on the QUIP-RS. Additionally, the ICDs total on the PICS was also tested, and

the result showed that UPP had a significant weak positive correlation with the ICDs total score on the PICS as well. Of interest, this correlation was not statistically significant for the original UPPS-P total score, *Table 28*. In addition, the correlation of the UPP was stronger than that of the UPPS-P total score (including all subscales) with the ICDs total score on both the QUIP-RS and PICs. Lastly, the UPP showed a significant weak positive correlation with 'other related ICBS', i.e. hobbyism-punding and DDS on the QUIP-RS and the hobbyism-punding on the PICS, as shown in *Table 31*.

Table 30 Correlation Between Personality Traits on the UPPS-P with Individual ICB on the QUIP-RS

	C. Gambling	**Hypersexuality**	**Binge eating**	**C. shopping**	**Hobbysm-punding**	**DDS**
	Spearman correlation coefficient *r (power for small effect size of .3 =.71), (*corrected α level* = .05/5= .01)**					
Negative Urgency **	**.338, *p* = .003**	.291, *p* = .012	.293, *p* = .012	.244, *p* = .038	**.348, *p* = .003**	**.313, *p* = .007**
Lack of Premeditation	.100, *p* = .3	-.016, *p* = .8	.045, *p* = .7	.153, *p* = .1	-.061, *p* = .6	-.008, *p* = .9
Lack of Perseverance	.211, *p* = .6	**.339, *p* = .003**	**.396,** *p* < **.001**	.241, *p* = .06	.061, *p* = .6	.172, *p* = .1
Sensation Seeking	-.121, *p* = .3	.067, *p* = .5	-.235, *p* = .045	-.104, *p* = .3	-.134, *p* = .2	-.048, *p* = .4
Positive Urgency	.200, *p* = .09	.195, *p* = .09	.215, *p* = .064	.216, *p* = .06	.282, *p* = .016	.266, p = .02

**The power for Spearman's correlation was calculated on SPSS for a small effect size (.3) =.71. ** For all 5 UPP-P subscales, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/5) =.01*

Table 31 Correlation of the UPP with ICDs Total and Other Related ICBs on QUIP-RS and PICS

	QUIP-RS ICDs total	PICS ICDs totals	QUIP-RS Hobbysm+Punding	QUIP-RS DDS	PICS Hobbysm+Punding	PICS DDS
	Spearman correlation coefficient *r, power for small size of .3 =.7, (α level = .05)**					
UPP	**.402, $p < .001$**	**.370, $p < .001$**	**.291, $p = .01$**	**.287, $p = .01$**	**.272, $p = .02$**	.117, $p = .3$

**The power for Spearman's correlation was calculated on SPSS for a small effect size (.3) =.71*

Summary Points: Regression Analysis at Baseline

- Impulsivity (ICDs total on the QUIP-RS) at baseline were predicted by Depression.
- Gambling scores were predicted by anhedonia, negative urgency and apathy.
- Hypersexuality scores were predicted by depression and elation.
- Binge eating scores were predicted by anxiety and depression.
- Hobbyism-Punding scores were predicted by depression.
- DDS scores were predicated by anxiety and apathy.
- Multiple ICDs were predicted by cognitive scores and negative urgency.

3.4.5 Regression Analysis at Baseline

For the ICD total, the overall regression was statistically significant (Adjusted $R^2 = .327$, F (2, 70) = 18.54, $p < .001$). It was found that depression on the PHQ-9 ($\beta = .624$, $p < .001$) and negative urgency on the UPPS-P ($\beta = .502$, $p = .002$) significantly predicted high ICDs total on the QUIP-RS at T0. For compulsive gambling, the overall regression was statistically significant (Adjusted $R^2 = .204$, F (3, 69) = 7.155, $p < .001$). It was found that the ability to experience pleasure on the SHAPS ($\beta = -.613$, $p = .014$), negative urgency on the UPPS-P ($\beta = .2.7$, $p = .003$), and apathy on the AES ($\beta = .154$, $p = .003$) significantly predicted high compulsive gambling scores on the QUIP-RS at T0. For hypersexuality, the overall regression was statistically significant (Adjusted $R^2 = .242$, F (2, 70) = 12.495, $p < .001$). It was found that depression on the PHQ-9 ($\beta = .182$, $p < .001$) and elation item on the NPI-19 ($\beta = 1.720$,

$p < .001$) significantly predicted high hypersexuality scores on the QUIP-RS at T0. For compulsive shopping, the overall regression was statistically significant (Adjusted $R^2 = .217$, F (2, 70) = 10.981, $p < .001$). It was found that anxiety on the GAD-7 ($\beta = .178$, $p = .008$) and depression on the PHQ-9 ($\beta = .144$, $p = .013$) significantly predicted high compulsive shopping scores on the QUIP-RS at T0. For binge eating, the overall regression was statistically significant (Adjusted $R^2 = .277$, F (2, 70) = 14.798, $p < .001$). It was found that anxiety on the GAD-7 ($\beta = .227$, $p = .005$) and depression on the PHQ-9 ($\beta = .220$, $p = .002$) significantly predicted high binge eating scores on the QUIP-RS at T0.

For hobbyism-punding, the simple regression was statistically significant ($R^2 = .190$, F (1, 71) = 16.647, $p < .001$). It was found that depression on the PHQ-9 ($\beta = .486$, $p < .001$) significantly predicted high hobbyism-punding scores on the QUIP-RS at T0. Positive urgency on the UPPS-P also showed a significant regression ($R^2 = .122$, F (1, 71) = 0.897, $p = .002$, $\beta = .281$, $p = .002$). However, when added to a multilinear model with depression, its corrected α level reduced to below the significance level ($\beta = .186$, $p = .039$).

For DDS, the overall regression was statistically significant (Adjusted $R^2 = .220$, F (2, 70) = 11.126, $p < .001$). It was found that anxiety on the GAD-7 ($\beta = .202$, $p = .008$) and apathy on AES ($\beta = .100$, $p = .010$) significantly predicted high DDS scores on the QUIP-RS at T0. For the multiple-ICD cases, the overall regression was statistically significant (Adjusted $R^2 = .245$, F (2, 70) = 2, $p < .001$). It was found that cognition on the PDQ-39 ($\beta = .074$, $p < .012$) and negative urgency on the UPPS-P ($\beta = .046$, $p = .004$) significantly predicted the frequency of multiple ICDs cases at T0.

Summary Points: Mood Symptoms at Baseline

- The frequency of clinically significant depression was 53% (n=38).
- Depression showed a significant moderate positive correlation with cognitive subdimension on the PDQ-39.
- The frequency of suicidality (cutoff=1) was 15% at the Baseline.
- The frequency of clinically significant anxiety was 16%.
- Anxiety showed a significant moderate positive correlation with the cognition subdimension on the PDQ-39.

3.4.6 Mood Symptoms at Baseline

The frequency of participants in clinically significant depression, suicidality, anxiety and apathy subgroups and the differences in their corresponding total score across gender, PD onset, LEDD median and retired/not working subgroups are displayed in *Table 32*. Mann-Whitney *U* test was suitable for analysing the difference. In addition, the correlation between mood symptoms with the PDQ-39, NPI-12, SHAPS, sleep hours and personality traits were investigated. The results are displayed in *Table 33*. Spearman correlation test was used for all questionnaires. Starting with depression measured by the PHQ-9, the frequency of clinically significant depression was 53% (n=38). The frequency was higher, but the total score did not differ significantly in the working, males, late PD onset, below median LEDD subgroups, and recruited-after-operation subgroup. In the former subgroup, the *p* value was nearly significant.

The PHQ-9 scores showed a significant moderate positive correlation with the PDQ-39 summary index and the total score on the pleasure scale (SHAPS) and a significant weak positive correlation with the NPI-12. Lastly, additional analysis was conducted to test the correlation of depression on the self-rated PHQ-9 with the depression-related items on the self-rated PDQ-39, emotional wellbeing subdimension (item 17-22) and the RF-rated UPDRS, I (item 3). The PHQ-9 showed a significant strong correlation of $r\ (73) = .668$, $p < 001$, with the emotional wellbeing subdimension on the PDQ-39 (corrected α level = .05/3=.016). It also showed a significant weak positive correlation of $r\ (73) = .317$, $p = .003$ (α level = .05) with the 3rd item on UPDRS, I. Lastly, the total score on the PHQ-9 showed a significant moderate

positive correlation with cognitive subdimension on the PDQ-39, r (73) = 502, p <.001 (corrected α level = .05/3=.016)

On the PHQ-9, item 9 was utilised for suicidality in the cohort at the T0. The frequency of suicidality (cutoff=1) was 15% at the T0, which was non-significantly higher in males, late-onset PD, above LEDD median and working participants. The suicidality showed a significant weak positive correlation with the NPI-12 total scores. Although, no correlation was found with the summary index of the PDQ-39 (total score/8), the Spearman correlation showed a significant weak positive correlation between suicidality and emotional wellbeing subdimension on PDQ-39 (item 17-22), r (73) = .381, p <.001 (corrected α level = .025). Further analyses were conducted using the same test for the correlation of total score on self-rated, suicidality-related item 9 on the PHQ-9 with the self-rated, cognition subdimension (item 30-33) on the PDQ-39 and the RF-rated, cognition-related item 1 on the UPDRS, I. The correlation was non-signficant weak positive r (73) = .126, p = .2 and r (73) = .137, p = .2 (corrected α level = .025) with both, respectively. Of note, the two cognitive-related variables had a significant moderate positive correlation, r (73) = .498 p <.001 (corrected α level = .025). Furthermore, the suicidality correlation with apathy (AES) was tested using Spearman correlation, which showed a significant weak positive r (73) = .247, p =.03, (α level = .05). Lastly, suicidality showed a very weak correlation with personality traits on the UPPS-P, which was not close to the significant level, *Table 33*.

As for anxiety, the total score on GAD-7 showed that 16% of the total participants scored above the cutoff point (>10), indicating clinically significant anxiety. The frequency was slightly higher in the males, late-onset PD, above median LEDD and working subgroups. However, the difference in total scores did not reach a significant level across any subgroups. Like depression scores on the PHQ-9, GAD-7 total scores showed a moderate positive correlation with the PDQ-9 and NPI-12 and a significant weak positive correlation with the total score on the pleasure scale (SHAPS). In the next step, the correlation was tested between the anxiety measured on the GAD-7 and the RF-rated UPDRS, 1 (item 4) and other anxiety-related items on the self-rated PDQ-39, emotional wellbeing subdimension, using Spearman correlation. The GAD-7 total score showed a significant strong positive correlation with the former, *r (73)* = .610, p <.001 (α level = .05) and a significant weak positive correlation with the latter, *r (73)* = .387, p = <001 (corrected α level = .05/3 = .016). Lastly, using the same test, a significant

moderate positive correlation was found between the total score on GAD-7 and the cognition subdimension on the PDQ-39, r (73) =.449, p <.001 (corrected α level = .016).

Table 32 Frequency Difference for Psychiatric Symptoms and Carer Burden in Pre-Defined Groups

	Total	**Gender**			**PD onset**		**LEDD Median**			**Working Status**			**Recruitment time**		
	(N=73)	♂ **(n=50)**	♀ **(n=23)**	**Mann Whitney *U***	**Early-onset (n=28)**	**Late Onset (n=30)**	**Mann Whitney *U***	**Below Median (n=28)**	**Above Median (n=30)**	**Mann Whitney *U***	**Retired (n=29)**	**Working (n=44)**	**Mann Whitney *U***	**Before Operation (n=50)**	**After operation * (n=15)**	**Mann Whitney *U***
							The α level = .05									
Depression (PHQ-9)	53%	56%	48%	$U = 517$, $p = .4$	42%	65%	$U = 802$, $p = .1$	57%	50%	$U = 723$, $p = .3$	45%	65%	$U = 468$, $p = .055$	50%	65%	$U = 516$, p = .2
Suicidality (PHQ-9)	15%	16%	13%	$U = 558$, $p = .7$	13%	17%	$U = 691$, $p = .6$	10%	19%	$U = 704$, $p = .6$	11%	22%	$U = 578$, $p = .2$	15%	13%	$U = 425$, $p = .8$
Anxiety (GAD-7)	16%	18%	13%	$U = 658$, $p = .3$	18%	14%	$U = 728$, $p = .4$	13%	19%	$U = 568$, $p = .2$	13%	20%	$U = 657$, $p = .8$	16%	26%	$U = 478$, $p = .5$
Apathy (AES)	29%	31%	23%	$U = 335$, $p = .5$	31%	25%	$U = 680$, $p = .8$	35%	25%	$U = 601$, $p = .4$	29%	27%	$U = 692$, $p = .5$	27%	33%	$U = 553$, $p = .1$
Pleasure (SHAPS)	34%	40%	21%	$U = 483$, P = .2	37%	31%	$U = 601$, $p = .4$	35%	33%	$U = 410$, $p = .7$	36%	31%	$U = 693$, $p = .5$	33%	40%	$U = 526$, $p = .1$

	Total (N=73)	Gender			PD onset			LEDD Median			Working Status			Recruitment time		
		♂ (n=50)	♀ (n=23)	Mann Whitney *U*	Early-onset (n=28)	Late Onset (n=30)	Mann Whitney *U*	Below Median (n=28)	Above Median (n=30)	Mann Whitney *U*	Retired (n=29)	Working (n=44)	Mann Whitney *U*	Before Operation (n=50)	After operation * (n=15)	Mann Whitney *U*
							The α level = .05									
Carer burden (ZBI) (n=58)	96%	100% (n=44)	95% (n=14)	$U = 318$, $p = .5$	92%	100%	$U = 487$, $p = .1$	100%	93%	$U = 487$, $p = .1$	100%	92%	$U = 354$, $p = .4$	-	-	-

**Recruitment after operation was completed before DBS activation.*

Table 33 Correlation Between Other Main Outcomes with Main Psychiatric Scales and Personality Traits.

	PDQ-39	**NPI-12**	**SHAPS**	**Sleep Hours**	**Personality Traits (UPPS-P)**				
					Negative Urgency	**Lack of premeditation**	**Lack of perseverance**	**Sensation seeking**	**Positive Urgency**
	Spearman correlation *r*, power* for small size of .3 =.7, *α level = .05*				***The corrected α level = .01****				
Depression (PHQ-9)	**.532, *p* = .001**	**.32, *p* = .005**	**.44, *p* = .001**	-.17, *p* = .1	**.37, *p* = .001**	.04, *p* = .7	.24, *p* = .03	-.12, *p* = .3	**.36, *p* = .001**
Suicidality (Item 9, PHQ-9)	.183, p = .1	**.245, *p* = .03**	.200, *p* = .090	-.076, *p* = .5	.044, *p* = .7	-.035, *p* = .7	.002, p = .9	.079, *p* = .5	.027, *p* = .8
Anxiety (GAD-7)	**.442, *p* = .001**	**.41, *p* = .001**	**.30, *p* = .008**	-.2, *p* = .8	.266, *p* = .02	-.07, *p* = .5	.25, *p* = .02	-.01, *p* = .9	.16, *p* = .1
Apathy (AES)	**.324, *p* = .005**	**.31, *p* = .007**	**.57, *p* = .001**	.01, *p* = .8	.26, *p* = .02	.18, *p* = .1	**.45, *p* = .001**	-.21, *p* = .06	.26, *p* = .02
Social & Work Adjustment (WSAS)	.165, *p* = .1	.16, *p* = .1	-.03, *p* = .7	.03, *p* = .8	-.02, *p* = .8	-.12, *p* = .3	-.007, *p* = .9	-.09, *p* = .4	.16, *p* = .16

	PDQ-39	NPI-12	SHAPS	Sleep Hours	Personality Traits (UPPS-P)				
					Negative Urgency	Lack of premeditation	Lack of perseverance	Sensation seeking	Positive Urgency
	Spearman correlation *r*, power* for small size of .3 =.7, *α level = .05*				***The corrected α level = .01****				
Quality of Life EQ-5D-5L VAS	**-.554, *p*<.001**	-.195, *p*=.09	-.082, *p*=.4	-.027, *p* =.8	-.196, *p*= .09	-.085, *p* =.4	-.221, *p* = .06	.094, *p* = .4	-.184, *p*=.1
Rx complication (UPDRS, IV)	.331, *p* = .004	**.33, *p* = .004**	.13, *p* = .2	-.04, *p* = .7	.08, *p* = .4	.18, *p* = .12	.18, *p* = .1	.12, *p* = .2	.07, *p* = .5
Carer burden (n=58) (ZBI)	**.46, *p* = .001**	**.32, *p* = .01**	-.11, *p* = .38	-.07, *p* = .6	.27, *p* = .03	-.11, *p* = .3	.15, *p* = .2	-.01, *p* = .8	.1, *p* = .4

**The power for Spearman's correlation was calculated on SPSS for a small effect size (.3) =.71 **For all 5 UPP-P subscales, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/5) =.01*

Summary Points: Apathy and Pleasure Experiencing Ability at Baseline

- The percentage of patients with clinical apathy was 28%.
- Apathy showed only a significant weak positive correlation with the PDQ-39 cognition subdimension.
- Depression showed a significant moderate positive correlation with anxiety and apathy total scores.
- 34% of the total participants scored above the cutoff for anhedonia.

3.4.7 Apathy and Pleasure Experiencing Ability at Baseline

The percentage of patients with clinically significant apathy (AES, cutoff=38) was 28%, which was higher in the males, early-onset, below the median LEDD, retired and after the operation subgroups, *Table 32*. For the former subgroup, the difference showed a trend towards statistical significance. Further analysis was carried out for the relationship of apathy measured on the AES with apathy-related items on the informant-rated NPI-12 (item 7, G) and the RF-rated UPDRS, I (item 5), in addition to cognition-related subdimension on the PDQ-39 (item 30-36) and UPDRS, I (item 1). The AES total score showed a significant weak positive correlation with the first two apathy-related items, $r\ (73)$ = .323, p =.003, and r (73) =.296, p = .011 (corrected α level = .05/3=.016). As for cognition-related items, it showed only a significant weak positive correlation r (73) = .345, p =003 with PDQ-39 cognition subdimension (corrected α *level* = .05/3=.016). In comparison to depression and anxiety, apathy (AES) showed a weak positive correlation with the PDQ-39 and NPI-12, but a significant moderate positive correlation with the total score on the pleasure scale (SHAPS).

Further analysis was conducted for the relationship between anxiety, depression, and apathy using the Spearman correlation. Depression showed a significant moderate positive correlation of r=.421, p <.001 and r=.517, p>.001 (corrected α level =.05/3=.016) with the GAD-7 and AES total scores. As for the ability to experience pleasure (anhedonia), 34% of the total participants scored above the cutoff. However, there was not a significant difference across the pre-defined groups.

3.4.8 Psychosis and Psychotic Symptoms at Baseline

At T0, the 4 patients who scored above 1 for the first two items on the NPI-12 were all males. Three of these participants were in the above LEDD median subgroup. However, 2 were in the early- and 2 in the late-onset subgroup. No further investigation was conducted for psychosis and psychotic symptoms at T0.

Summary Points: Personality Traits at Baseline

- The Depression scores showed a significant weak positive correlation with negative urgency and positive urgency traits.
- Apathy showed a weak to moderate correlation with lack of perseverance, lack of medication and positive urgency traits.

3.4.9 Personality Traits at Baseline

In this section, the result of a further investigation into the relationship between personality traits and psychiatric symptoms and QoL is presented. The PHQ-9 total score showed a significant weak positive correlation with negative urgency and positive urgency, *Table 33*. However, the GAD-7 total score showed a trend towards a significant weak positive correlation with negative urgency and the lack of perseverance. The other two traits, the lack of premeditation and sensation seeking, did not show such a correlation. As for apathy, the total score on the AES showed a similar weak to moderate correlation with the same lack of perseverance, lack of medication and positive urgency. However, the correlation was significant only for the former. For the latter two traits, it was nearly significant. As for the QoL and neuropsychiatric inventory, a correlation analysis was conducted for the PDQ-39 and NPI-12 total scores with all personality traits. Negative urgency, lack of perseverance, and positive urgency showed a significant weak, positive, or moderate correlation with the PDQ-39 summary index. However, these traits only showed a trend towards a significant weak positive correlation with the NPI-12 scores. Of note, the lack of premeditation and sensation seeking did not show any meaningful correlation with any of the main outcomes, as displayed in *Table 33*.

Table 34 Correlation Between Personality Traits and QoL and Neuropsychiatric Inventory

	PDQ-39 total score	**NPI-12 total score**
	Spearman correlation *r*	
	power* for small size of .3 =.7.	
	The corrected α level = 0.5/5= .01	
Negative Urgency	**.402, *p* < .001**	.267, *p* = .02
Lack of premeditation	.161, *p* = .1	.138, *p* = .2
Lack of perseverance	.254, *p* =.03	.265, *p* = .02
Sensation seeking	-.003, *p* = .9	-.079, *p* = .5
Positive urgency	**.411, *p* < .001**	.204, *p* = .08

**The power for Spearman's correlation was calculated on SPSS for a small effect size (.3) =.71*

In the final step, the UPPS-P results at T0 were analysed to investigate in-between traits correlation. Results are presented in *Table 35*. Sensation seeking showed a trend towards a significant correlation with lack of premeditation and positive urgency, while positive urgency showed a significant strong, moderate, and weak positive correlation with negative urgency, lack of premeditation and lack of perseverance, respectively.

Table 35 Correlation Between Personality Traits on the UPPS-P

	Negative Urgency	**Lack of Premeditation**	**Lack of Perseverance**	**Sensation Seeking**
	Spearman correlation *r* power* for a small size of .3 =.7. ***The corrected α level = 0.5/5= .01***			
Negative Urgency	-	-	-	-
Lack of premeditation	.188, p = .1	-	-	-
Lack of perseverance	**.373, p = .001**	**.553, p < .001**	-	-
Sensation seeking	.013, p = .9	.233, p = .047	-.055, p = .6	-
Positive urgency	**.768, p < .001**	**.400, p < .001**	**.374, p = .001**	.204, p = .08

**The power for Spearman's correlation was calculated on SPSS for a small effect size (.3) =.71*

3.4.10 Data Analysis for Primary and Secondary Outcomes at T2

In this section, a thorough analysis is presented of the changes observed in impulsive behaviours, psychiatric comorbidities, and other outcomes of interest. All demographic details and medication information of participants who completed the T2 are displayed in *Table* 19 and*Table* 21. In addition, the results for outcomes are displayed in *Table* 26.

1 out of 73 participants dropped out of the study without being questioned about their decision. Of the remaining 72 recruited participants included in this thesis, 61 completed the T2. For these 61 participants, only 44 carers completed their scales, dropping from 58 at the T0.

Summary Points: The Frequency of Positive Cases of ICBs Across Pre-defined Groups at T2

- The frequency of positive cases of individual ICBs was reduced.
- The frequency of cases of the ICDs total remained higher in males, late-onset, and below the median LEDD subgroups.
- The frequency of ICDs total positive cases remained higher in retired, non-DA users and psychotropic users.

3.4.10.1 The Frequency of Positive Cases of ICBs Across Pre-defined Groups at T2

Only the frequency of positive cases at T2 will be presented in this section. *Table 36* includes a frequency comparison for positive cases between T0 *vs* T2 and a breakdown of the frequency of participants who scored above the corresponding cutoff point (positive cases) for individual ICBs, in addition to the frequency difference in gender, PD onset and LEDD median groups. *Table 37* displays the results for the ICDs total on the QUIP-RS and PICs and results for the other related ICBs at the T2. The results of measured impulsivity on the QUIP-RS are presented in this section. The frequency of positive cases of the ICDs total remained non-significantly higher in males, late-onset, and below the median LEDD subgroups.

As for individual ICBs, the frequency of positive cases was reduced for all. The difference in total score for hypersexuality remained significant across gender subgroups. Furthermore, the frequency of positive cases of compulsive shopping reduced to 0% for both genders. Additionally, the frequency of positive cases of hypersexuality in females remained unchanged at 0%, but not for compulsive gambling, which increased from 0% to 5.9% (n=1). Similarly, the frequency of positive cases of binge eating was reduced more in males than in females. Both ICDs and hobbyism-punding showed a trend towards a higher frequency in the relatively smaller female subgroup (n=17). As for PD onset, compared to T0, at T2, the frequency of positive cases of binge eating and hobbyism was lower in the late-onset PD subgroup. For other ICBs, the difference remained unchanged. No significant differences were found in their total scores across the subgroups. Regarding the LEDD median groups, all but DDS remained the

same as at T0, or the frequency of positive cases was higher in the above LEDD median subgroup. However, none significantly differed in the total scores across the subgroups.

Moreover, as shown in *Table 37*, the frequency of ICDs total positive cases remained higher in retired, non-DA users and psychotropic users. The difference in total scores across the subgroups was non-significant. As for the DA Use group, the frequency of binge eating increased from the T0 without a remarkable difference between DA users and non-DA users. However, in the non-DA user subgroup, the difference in the total score for DDS was almost significantly higher. Lastly, despite the drop in their number from the T0 (n=26 *vs* n=50), the frequency of positive cases of all ICBs was higher in the psychotropic user subgroup. The total scores, however, were non-significantly different.

Table 38 displays results for the differences in positive cases of ICBs in the clinically significant anxiety, depression, and apathy groups. Since only 5 patients out of 61 scored above the cutoff point on the GAD-7 at T2, the frequency difference across the clinically significant anxiety subgroups was not conducted. As for depression, except for compulsive gambling, the frequency of positive cases for all ICBs was higher in the clinically significant depression subgroup. In the same group, the same differences were nearly significant for total scores of ICDs total, binge eating and hobbyism-punding. In addition, the same difference was relatively close to a significant level for DDS. Of interest, although no positive cases of compulsive shopping were recorded, its total score was significantly higher in the clinically significant depression subgroup. Like anxiety subgroups, further analysis was not conducted for apathy as the number of participants who scored below the cutoff point was very small (n=2).

Table 36 The Frequency of Positive Impulsivity Across Gender, PD Onset and LEDD Median Groups at 6-month Follow-up

scales		Total T2	Gender			PD onset			LEDD Median		
	Total at T0 (N=73)	(N=61)	♂ (n=44)	♀ (n=17)	Difference (Mann-Whitney *U*)	Early-onset <50 (n=31)	Late-Onset >50 (n=30)	Difference (Mann-Whitney *U*)	Below Median <1103 (n=31)	Above median >1103 (n=30)	Difference (Mann-Whitney *U*)
			The α level (05/4) =.0125 for individual ICDs, and for other related ICBs: 0.05								
*ICDs **	QUIP-RS	26%	27%	29%	23%	$U = 365$, $p = .8$	25.8	30%	$U = 494$, $p = .6$	32%	23%	$U = 422$, $p = .6$
	PICS	12.3%	3.3%	12%	13%	$U = 480$, $p = .04$	3.2%	3.3%	$U = 539$, $p = .2$	6.5%	0%	$U = 505$, $p = 7$
Gambling	QUIP-RS	5.5%	4.9%	4.5	5.9%	$U = 331$, $p = .1$	3.2%	6.7%	$U = 490$, $p = .4$	9.7%	0%	$U = 412$, $p = .6$
	PICS	1.4%	1.6%	2%	0%	$U = 319$, $p = .4$	3.2%	0%	$U = 481$, $p = .6$	3.2%	0%	$U = 512$, $p = .7$
Hypersexuality	QUIP-RS	6.8%	1.6%	2.3%	0%	**$U = 193$, $p = .002$**	0%	3.3%	$U = 498$, $p = .5$	3.2%	0%	$U = 493$, $p = .5$
	PICS	4.1%	1.6%	6%	0%	$U = 229$, $p = .3$	0%	3.3%	$U = 480$, $p = .3$	0%	3.3%	$U = 520$, $p = .5$
	QUIP-RS	17.8%	13.1%	11.4	17.6%	$U = 409$, $p = .5$	13.3	12.9	$U = 521$, $p = .3$	16.1%	10%	$U = 465$, $p = 4$

	scales	Total at T0 (N=73)	Total T2 (N=61)	Gender			PD onset			LEDD Median		
				♂ (n=44)	♀ (n=17)	Difference (Mann-Whitney *U*)	Early-onset <50 (n=31)	Late-Onset >50 (n=30)	Difference (Mann-Whitney *U*)	Below Median <1103 (n=31)	Above median >1103 (n=30)	Difference (Mann-Whitney *U*)
				The α level (05/4) =.0125 for individual ICDs, and for other related ICBs: 0.05								
Binge Eating	PICS	9.6%	11.5%	8%	13%	*U* =477, *p* = .03	16.1%	6.7%	*U* = 485, *p* = .7	19.4%	3.3%	*U* = 393, *p* = .4
Compulsive Shopping	QUIP-RS	4.1%	0%	-	-	*U*=477, *p* = .07	-	-	*U* = 416, *p* = .4	-	-	*U* = 512, *p* = .7
	PICS	0%	0%	-	-	*U*= 314, *p* = .6	-	*U* =465, *p* = 1.	*U* = 522, *p* = 1.	-	-	*U* = 494, *p* = 9
Hobbysm+Punding	QUIP-RS	32%	27.9%	22.7%	41.2%	*U =410, p = .1*	35.5%	20%	*U* = 433, *p* = .6	32%	23%	*U* = 380, *p* = 9
	PICS	4.1%	3.3%	0%	13%	*U*= 310, *p* = .08	0%	6.7%	*U =511, p = .07*	6.5%	0%	*U* = 420, *p* = .08
DDS	QUIP-RS	16 %	8.2%	6.8%	11.8%	*U*= 355, *p* = .8	12.9%	3.3%	-	6.5%	10%	*U* = 320, *p* = 8
	PICS	0%	0%	-	-	*U*= 224, *p* = .9	-	-	*U* = 465, *p* = 1.	-	-	*U* = 416, *p* = .5

*LEDD = Levodopa Equivalent Daily Dose, QUIP-RS= the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, DDS= Dopamine Dysregulation Syndrome ICDs= Impulsive Control Disorders, PICS= The Parkinson's Impulse-Control Scale. The effect size for the statistically significant result was calculated using the following equation ($r^2 = z^2/n - 1$) in Excel. Z stands for standardised test statistic ** For ICDs total, compulsive gambling, hypersexuality, binge eating and compulsive shopping the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/4) =.0125*

Table 37 The Frequency of Positive Impulsivity in DA Use and Psychotropic Use Groups

	Scales	Total (N=61)	Working Status (Retired?)			DA Use			Psychotropics user		
			Yes (n=34)	No (n=27)	Difference (Mann-Whitney U)	Yes (n=28)	No (n=33)	Difference (Mann-Whitney U)	Yes (n=26)	No (n=35)	Difference (Mann-Whitney U)
			The α level (05/4) =.0125 for individual ICDs, and for other related ICBs: 0.05								
*ICDs **	**QUIP-RS**	27%	30%	26%	*U =449, p = .8*	25%	30%	*U =380, p =.2*	35%	23%	*U =501, p = .4*
	PICS	3.3%	5.9%	0%	*U =461, p = .9*	0%	6%	*U =408, p =.2*	4%	3%	*U =467, p =.8*
Gambling	**QUIP-RS**	4.9%	3%	7%	*U =465, p = .8*	7%	3%	*U =449, p =.7*	8%	3%	*U =489, p =.4*
	PICS	1.6%	2.9%	0%	*U* = 467, *p* = .7	0%	3%	*U =453, p =.*	3.8%	0%	*U =453, p =.7*
Hypersexuality	**QUIP-RS**	1.6%	0%	3.7%	*U* = 442, *p* = .2	0%	3%	*U =395, p =.3*	3.8%	0%	*U =442, p =.8*
	PICS	1.6%	0%	3.7%	*U* = 494, *p* = .6	0%	3%	*U =448, p =.3*	0%	2.9%	*U =442, p =3*
Binge Eating	**QUIP-RS**	13.1%	12%	15%	*U* = 447, *p* = .8	11%	15%	*U =400, p =.3*	19%	9%	*U =509, p = .4*
	PICS	11.5%	14.7%	7.4%	*U =501, p = .4*	11%	12%	*U =396, p =.2*	15.4%	8.6%	*U =477, p = .6*
	QUIP-RS	0%	-	-	*U* = .523, *p* = .6	-	-	*U =408, p =.2*	-	-	*U =486, p = .6*

	Scales	Total (N=61)	Working Status (Retired?)			DA Use			Psychotropics user		
			Yes (n=34)	No (n=27)	Difference (Mann-Whitney U)	Yes (n=28)	No (n=33)	Difference (Mann-Whitney U)	Yes (n=26)	No (n=35)	Difference (Mann-Whitney U)
			The α level (05/4) =.0125 for individual ICDs, and for other related ICBs: 0.05								
Compulsive Shopping	**PICS**	0%	-	-	*U* = 459, *p* = .1.	-	-	*U =462, p =1.*	-	-	*U =455, p = 1.*
Hobbysm+Punding	**QUIP-RS**	27.9%	29%	26%	*U* = 478, *p* = .7	25%	30%	*U =451, p =.8*	27%	29%	*U =496, p =.5*
	PICS	3.3%	2.9%	3.7%%	*U* = 439, *p* = .4	3%	3.6%	*U =450, p =.6*	3.8%	2.9%	*U =446, p =.7*
DDS	**QUIP-RS**	8.2%	5.9%	11%	*U =452, p = .9.*	0%	15%	*U =353, p =.07*	11%	6%	*U =546, p =.1*
	PICS	0%	-	-	*U =459, p = 1.*	-	-	*U =462, p =1.*	-	-	*U =455, p =1.*

*QUIP-RS= the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, DDS= Dopamine Dysregulation Syndrome ICDs= Impulsive Control Disorders, PICS= The Parkinson's Impulse-Control Scale, the Effect size for statistically significant result was calculated using following equation ($r^2 = z^2/n - 1$) in Excel. Z stands for standardised test statistic. *For ICDs total, compulsive gambling, hypersexuality, binge eating and compulsive shopping the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/5) =.01*

Table 38 The Frequency of Positive Impulsivity in Clinically Significant Depression, Anxiety and Apathy Groups

	Scale	Total T2 (N=61)	Anxiety (GAD-7, cutoff=10) + (n=5)	Anxiety (GAD-7, cutoff=10) - (n=56)	Anxiety (GAD-7, cutoff=10) Difference (Mann-Whitney U)	Depression (PHQ-9, cutoff=9) + (n=21)	Depression (PHQ-9, cutoff=9) - (n=40)	Depression (PHQ-9, cutoff=9) Difference (Mann-Whitney U)	Apathy (AES, cutoff=38) Yes (n=59)	Apathy (AES, cutoff=38) No (n=2)	Apathy (AES, cutoff=38) Difference (Mann-Whitney U)
			The α level (05/4) =.0125 for individual ICDs, and for other related ICBs: 0.05								
*ICDs **	QUIP-RS	27%	40%	26%	-	47.6%	17.5%	***U* = 585, *p* = .01**	27%	50%	-
	PICS	3.3%	20%	1.8%	-	4.8%	2.5%	*U* = 485, *p* = .2	-	-	-
Gambling	QUIP-RS	4.9%	20%	3.6%	-	2.5%	9.5%	*U* = 480, *p* = .1	5.1%	0%	-
	PICS	1.6%	0%	1.8%	-	4.8%	0%	*U* = 400, *p* = .5	-	-	-
Hypersexuality	QUIP-RS	1.6%	0%	1.8%	-	0%	2.5%	*U* = 449, *p* = .6	1.7%	0%	-
	PICS	1.6%	0%	1.8%	-	4.8%	0%	*U* = 440, *p* = .1	-	-	-
Binge Eating	QUIP-RS	13.1%	20%	12.5%	-	28.6%	5%	*U* = 580, *p* = .014	13.6%	0%	-
	PICS	11.5%	0%	12.5%	-	19%	7.5%	*U* = 485, *p* = .2	-	-	-
Compulsive Shopping	QUIP-RS	0%	-	-	-	-	-	-	-	-	-

	Scale	Total T2 (N=61)	Anxiety (GAD-7, cutoff=10) + (n=5)	Anxiety (GAD-7, cutoff=10) - (n=56)	Anxiety (GAD-7, cutoff=10) Difference (Mann-Whitney U)	Depression (PHQ-9, cutoff=9) + (n=21)	Depression (PHQ-9, cutoff=9) - (n=40)	Depression (PHQ-9, cutoff=9) Difference (Mann-Whitney U)	Apathy (AES, cutoff=38) Yes (n=59)	Apathy (AES, cutoff=38) No (n=2)	Apathy (AES, cutoff=38) Difference (Mann-Whitney U)
					The α level (05/4) =.0125 for individual ICDs, and for other related ICBs: 0.05						
Hobbysm+Punding	PICS	0%	-	-	-	-	-	$U = 420$, $p = 1.$	-	-	-
	QUIP-RS	27.9%	60%	25%	-	47%	17.5%	***U* = 577, *p* = .01**	27%	50%	-
	PICS	3.3%	40%	-	-	4.8%	2.5%	$U = 419$, $p = .9$	0%	5.8%	-
DDS	QUIP-RS	8.2%	0%	8.9%	-	19%	2.1%	$U = 521$, $p = .08$	8.5%	0%	-
	PICS	0%	-	-	-	-	-	$U = 420$, $p = 1.$	-	-	-

*QUIP-RS= the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, DDS= Dopamine Dysregulation Syndrome ICDs= Impulsive Control Disorders, PICS= The Parkinson's Impulse-Control Scale, the Effect size for statistically significant result was calculated using following equation ($r^2 = z^2/n - 1$) in Excel. Z stands for standardised test statistic. *For ICDs total, compulsive gambling, hypersexuality, binge eating and compulsive shopping the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/5) =.01*

Summary Points: The T0-T2 Difference for Impulsivity

- The improvement was statistically significant for hobbyism-punding and hypersexuality.
- The improvement in DDS was followed by compulsive shopping in showing a trend towards a significant level.
- the Improvement in hypersexuality and hobbyism-punding was significantly different only across gender subgroups at the T2.
- The number of cases with multiple ICDs declines significantly at T2.

3.4.10.2 The T0-T2 Difference for Impulsivity

The results of testing for the T0-T2 difference in impulsivity are shown in *Table 39*. The Wilcoxon sign rank test was chosen for this purpose. The T0-T2 difference was statistically significant for hobbyism-punding and hypersexuality. Other items on the QUIP-RS showed differences which were variably close to the significance level. The T0-T2 difference in DDS was followed by compulsive shopping in showing a trend towards a significant change (after correction of α level). An analysis was conducted to compare the T0-T2 difference in hobbyism-punding and hypersexuality in gender, PD onset and working status groups; as shown in *Table 40*, the T0-T2 difference in hypersexuality and hobbyism-punding was significantly different only across gender subgroups at the T2. Using Spearman correlation, further investigation was conducted to understand the relationship between the T0-T2 difference in the ICBs that were significant or showed a trend towards the significant level and the difference in depression, anxiety, and apathy with a corrected α level of *.01*. The T0-T2 difference in ICDs total showed a significant weak positive correlation with the T0-T2 difference in apathy (AES) at the T2 follow up, r (61) = .388, p = .002. It also showed a nearly significant weak positive correlation with the T0-T2 difference in depression (PHQ-9), r (61) =.297, p = .02.

Similarly, compulsive shopping showed a significant weak positive correlation with the T0-T2 difference in apathy (AES), r (61) = .357, p = .005. However, hypersexuality only showed a

weak positive correlation with T0-T2 difference in anxiety (GAD-7), which was relatively close to the significant level, r (61) = .254, p = .04. Of note, among all measured ICBs, only the difference of hobbyism-punding and compulsive shopping showed a significant moderate correlation r (61) = .560, p <.001. Lastly, the number of cases with multiple ICDs declines significantly at T2. This test was conducted using the Wilcoxon sign rank as the difference had an asymmetric distribution, Z = -2.25, p = 0.02 (effect size= .28).

Table 39 The T0-T2 Difference for ICBs

	T0-T2 difference Wilcoxon sign rank	**Sign.**	**Effect Size**
The corrected *α level: ICDs= .05/4 =.0125, ICD total and other related ICBs=.05*			
The ICDs Total	*Z* = -2	***P* = .045**	.25
Compulsive Gambling	*Z*= .28	*P* =.7	.03
Hypersexuality	***Z*=-2.5**	***P* = .012**	.28
Compulsive Shopping	*Z*=1.9	*P* = .04	.25
Binge Eating	*Z* =1	*P* = .3	.12
Hobbyism-Punding	***Z* =-2.85**	***P* =.004**	.36
DDS	*Z* =-1.86	*P* =.06	.23

** For ICDs total, compulsive gambling, hypersexuality, binge eating and compulsive shopping the following formula was applied for α level correction: (α altered =.05/4) =.0125. The effect size for Wilcoxon sing rank was calculated in Excel using r = z/√N.*

Table 40 The T0-T2 Difference Across Gender, PD Onset and Working Status Groups

	Gender				**PD onset**				**Working status**			
	Male (n=44)	**Female (n=17)**	***P* value**	**Effect size**	**Early onset (n=31)**	**Late-Onset (n=30)**	***P* value**	**Effect size**	**Retired (n=34)**	**Working (n=27)**	***P* value**	**Effect size**
	The corrected *α level: ICBs = .05/3 =.0125, ICD total and the related ICB=.05*											
The ICDs total	*t*=1.1, 95% *CI*: [1.8, 6.7], *df*=59		.255	.3	*t*=-1.7, 95% *CI*: [--7, .5], *df*=59		.09	.4	*t*=-1.4, 95% *CI*: [-.6.8, 1], *df*=59		.1	.3
Hypersexuality	**U=-.4**		**.6**	**.003**	U=.460		.6	.35	*t*=-.2, 95% *CI*: [-.1, .8], *df*=56		.07	.7
Compulsive Shopping	*t*=.2, 95% *CI*: [-.1.3,1.6], *df*=59		.8	.07	*t*=.7, 95% *CI*: [-2.2,.3] *df*=59		.1	-.03	*t*=.-.2, 95% *CI*: -.1,.6], *df*=59		.8	-.06
Hobbyism-Punding	**U=-.4**		**.6**	**.003**	*t*=-1.7, 95% *CI*: [-.5, .2], *df*=59		.7	.4	*t*=-242, 95% *CI*: [-.1.8, 1], *df*=59		.8	.06

**For ICDs total, hypersexuality compulsive shopping and hobbyism-punding across subgroups the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/3) =0.0125*

Summary Points: Correlation of Differences in Impulsivity with Other Outcomes at T2

- The improvement in anxiety showed a significant weak positive correlation with the improvement the ICDs total and hypersexuality.
- The worsening in apathy showed a significant weak positive correlation with the improvement in the ICDs total and hypersexuality.
- The PD duration & age did not show a significant correlation with the improvement of the ICDs total.
- The improvement in quality of life was not significantly correlated with the improvement in all measured ICBs.

3.4.10.3 Correlation of Differences in Impulsivity with Other Outcomes

The Pearson correlation coefficient was used to investigate further the relationship between the T0-T2 difference in impulsivity with demographics and the T0-T2 differences in total LEDD and other outcomes. The power for Pearson correlation was calculated on the SPSS software (.74). The only item in *Table 41* that required the Spearman correlation coefficient was the T0-T2 difference in total LEDD. The corrected α levels and p values for different scales can be found in the same table. Of note, these analyses were only conducted for the T0-T2 difference in ICDs total, hypersexuality and hobbyism-punding. This is because only these items on the QUIP-RS were significantly different at T2. Age at operation did not correlate significantly or nearly significantly with the T0-T2 differences in the measured impulsivities.

In comparison, the PD duration showed a weak negative correlation with the difference in the ICDs total. However, this correlation was only nearly significant. The difference in anxiety at the T2 showed a significant weak positive correlation with the T0-T2 differences of the ICDs total and hypersexuality, indicating a reduction in anxiety to be positively correlated with the reduction of the measured impulsivity's severity.

Furthermore, the T0-T2 difference in apathy showed a significant weak positive correlation with the difference in the ICDs total and hypersexuality. However, in *de novo* cases of apathy, no correlation was found between the T0-T2 difference in apathy scores on the AES and the improved ICBs on the QUIP-RS. The noteworthy correlation between the T0-T2 difference in quality of life measured on the PDQ-39 and the EQ-VAS was nonsignificant with the T0-T2

difference in all measured ICBs. Regarding T0-T2 differences in the UPDRS parts at the T2, the T0-T2 difference in the UPDRS, II showed a significant weak positive correlation with the T0-T2 difference in the ICDs total. In addition, the UPDRS, I and IV showed a nearly significant weak to very weak positive correlation with the T0-T2 difference in hobbyism-punding, respectively.

Table 41 Correlation of T0-T2 Difference in the Improved Impulsivities with Other Outcomes

	The ICDs Total		**Hypersexuality ***		**Hobbyism-punding**	
	Pearson correlation *r*	***p* value**	**Pearson correlation *r***	***p* value**	**Pearson correlation *r***	***P* value**
	The α level: 0.05		**Corrected α level: 0.025**		**The α level: 0.05**	
Age at operation	.031	.8	-.092	.4	.055	.6
PD duration	**-.296**	**.02**	-.139	.2	-.152	.2
*T0-T2 Difference LEDD * (spearman)*	-.218	.09	-.153	.2	.06	.6
T0-T2 Difference GAD-7	**.340,**	**.007**	**.342**	**.007**	.234	.4
T0-T2 Difference PDQ-39	.203	.1	-.106	.4	.186	.3
T0-T2 Difference apathy	**.377**	**.003**	**.281**	**.02**	.242	.2
T0-T2 Difference apathy (de novo cases n=43)	.141	.3	.120	.4	.101	.5
T0-T2 Difference EQ-VAS	.049	.7	-.142	.2	**-.027**	**.02**
UPDRS						
T0-T2 Difference UPDRS, I	.195	.1	.169	.1	**.265**	**.04**
T0-T2 Difference UPDRS, II	.230	.07	.00	1	.215	.3

	The ICDs Total		Hypersexuality *		Hobbyism-punding	
	Pearson correlation *r*	***p* value**	**Pearson correlation *r***	***p* value**	**Pearson correlation *r***	***P* value**
	The α level: 0.05		**Corrected α level: 0.025**		**The α level: 0.05**	
T0-T2 Difference UPDRS, IV	-.093	.4	.102	.4	**.029**	**.02**
T0-T2 Difference UPPS-P total	.216	.09	.133	.3	.072	.06
T0-T2 Difference UPP	.239	.06	.168	.1	.168	.168
T0-T2 Difference Negative Urgency	.193	.1	.178	.1	.083	.5
T0-T2 Difference Lack of premeditation	.09	.4	-.154	.2	.157	.157
T0-T2 Difference Lack of perseverance	.235	.06	.097	.4	.188	.1
T0-T2 Difference Sensation Seeking	.018	.8	.103	.4	**-.24**	**.04**
T0-T2 Difference Lack of positive urgency	.193	.1	.125	.3	.171	.1

**For hypersexuality, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/2) =.025*

3.4.10.4 Correlation of Change in Impulsivity and Personality Traits

The results are displayed in *Table 41*. The T0-T2 difference in sensation seeking showed a weak negative correlation with the hobbyism-punding difference, a trend towards the significance level. In addition, the difference in the total score of UPPS-P showed a weak to very weak positive correlation with all measured differences in ICBs. However, none reached the significance level except for the T0-T2 difference in the UPP and the lack of perseverance with the T0-T2 difference in the ICDs total. Of interest, the T0-T2 difference in negative

urgency showed a trend towards a weak positive correlation with the T0-T2 difference in the frequency of multiple ICD cases.

Summary Points: Regression Analysis for Impulsivity at T2

- Improvement in the ICD total was predicted at T2 by baseline anhedonia.
- Improvement in the hypersexuality was predicted at T2 by baseline elation scores.
- Improvement in hobbyism-punding was predicted at T2 by baseline anhedonia.
- Decline in multiple ICDs was predicated at T2 separately by baseline anhedonia and negative urgency (simple linear regression).

3.4.10.5 Regression Analysis for Impulsivity at T2

For the T0-T2 difference in ICD total, the overall regression was statistically significant (Adjusted R^2 = .474, F (2, 58) = 28.002, p < .001). It was found that the ability to experience pleasure on the SHAPS (β = 1.298, p = .001), adjusted for the T0 ICDs total, significantly predicted improvement in the ICD total on the QUIP-RS at T2. For the T0-T2 difference in hypersexuality, the overall regression was statistically significant (Adjusted R^2 = .518, F (3, 57) = 22.465, p < .001). It was found that elation items on the NPI-12 (β = 1.293, p = .002) and anhedonia on the SHAPS (β = .229, p = .047), adjusted for the T0 hypersexuality scores on the QUIP-RS, significantly predicted improvement in hypersexuality on the QUIP-RS at T2. For the T0-T2 difference in hobbyism-punding, the overall regression was statistically significant (Adjusted R^2 = .519, F (2, 58) = 22.465, p < .001). It was found that anhedonia scores on the SHAPS (β = .624, p = .02), adjusted for the T0 hobbyism-punding scores on the QUIP-RS, significantly predicted improvement in hobbyism-punding at T2. In simple linear regression, sensation seeking on the UPPS-P showed a trend of prediction of the T0-T2 difference in hobbyism-punding (R^2 = .08, F (1, 59) = 5.116, p =.02). In two simple linear regression analysis, anhedonia on the SHAPS (R^2 = .09, F (1, 59) = 6.345, p =.014) and negative urgency

on the UPPS-P (R^2 = .08, F (1, 59) = 5.608, p =.02) at T0 predicted the improvement in number of multiple ICDs cases at T2.

Summary Points: De Novo Cases of ICBs at T2

- There were 9 cases of *De novo* cases of ICBs
- Hobbyism-punding, binge eating, and DDS were the most frequent *de novo* ICBs, successively.
- No participants had more than 1 *De novo* ICBs
- Depression, cognition and anxiety were worse in *de novo* cases.

3.4.10.6 De Novo Cases of ICBs at T2

Finally, the frequency of de novo cases of ICBs is presented in *Table 42*. Hobbyism-punding, binge eating, and DDS were the most frequent *de novo* ICBs, successively. No participant had more than 1 *de novo* ICD. As for ICDs, only 1 male and 1 female had more than 1. For all ICBs, however, only 1 male and 1 female had more than 2 *de novo* ICBs at T2. Due to their small number, Mann Whitney *U* test was used to investigate if the following characters and outcomes are significantly different between the *de novo* ICBs (n=7) and the rest of the cohort (n=54): age at operation, age at diagnosis, PD duration, total LEDD, Anxiety (GAD-7), motor complications (UPDRS, IV), depression (PHQ-9), apathy (AES), anhedonia (SHAPS), cognition (PDQ-39), and personality traits (UPPS-P). Only T2 scores for cognition, U = 276.5, p = .046 (effect size = 0.06), depression, U = 285, p = .028 (effect size = 0.07) and anxiety, U = 284.5, p = .028 (effect size = 0.08) showed to be significantly higher in *de novo* cases.

Table 42 Frequency of De Novo Cases at T2

***De novo* cases of ICBs**	**n=**	**Gender**		**%**
		M	**F**	
		n=	**n=**	
The ICDs Total *	4	2	2	6.5%
Compulsive Gambling	1	0	1	1.6%

Hypersexuality	0	0	0	0%
Binge Eating	3	2	1	4.9%
Compulsive shopping	0	0	0	0%
Hobbyism-Punding	3	2	1	4.9%
DDS	2	1	1	3.2
Total ICBs (ICDs + other related ICBs)	9	5	4	14.6%

Summary Points: The T0-T2 Difference in Other Psychiatric and Quality of Life Outcomes at T2

- Quality of life significantly improved
- LEDD significantly reduced.
- Depression did not change significantly.
- Apathy worsened.

3.4.10.7 The T0-T2 Difference in Other Psychiatric and Quality of Life Outcomes at T2

The results for T0-T2 differences of all other measured outcomes at T2 and their significance are displayed in *Table 43*. The corrected α levels and p values for different scales can be found in the same table. The total LEDD significantly reduced from T0. The same was observed for anxiety (GAD-7). Similarly, the improvement in scores of the NPI-12 and its psychosis-related items was statistically significant. However, no significant change was observed for depression on the (PHQ-9) and emotional wellbeing subdimension on the PDQ-39. Apathy, on the other hand, showed a significant worsening. The Spearman correlation was utilised to examine the relationship between T2 apathy, cogitation, total LEDD, and impulsivity. The T2 apathy scores on the AES only showed a significant negative moderate correlation with cognition subdimension on PDQ-39 r (61) = -.411, p = .003.

Regarding suicidality, the result shows a non-significant reduction at T2. As for scales measuring the QoL, the total score on the PDQ-39 significantly improved, but improvement in the EQ-VAS nearly reached a significant level. On the PDQ-39, the significance of the difference (change) in the stigma and cognition subdimension at the T2 was analysed. There was a significant change in the former, but the latter. As for the three parts of the UPDRS, parts II and IV showed a significant improvement, while for part I, the improvement nearly reached significance. In addition, the total hours of sleep, measured on the UPDRS, IV, significantly improved.

Table 43 The T0-T2 Difference for LEDD, other psychiatric symptoms, Personality traits and Carer's burden

	Test used	**T0-T2 Difference**	**Sign.**	**Effect Size !**
		***The* α Level: .05, Except of items with ***		
Total LEDD ★	Wilcoxon sign Rank	*Z* = *-5*	***P* < .001**	.7
Anxiety (GAD-7)	Wilcoxon sign Rank	*Z* = -4.1	***P* < .001**	.52
Depression (PHQ-9)	Wilcoxon sign Rank	*Z* = -1.2	*P* = .1	.15
Suicidality	Wilcoxon Sing Rank	*Z* = *-.5*	*P* = .6	.12
Apathy (AES)	Wilcoxon sign Rank	*Z* = 6.1	**P < .001**	.7
NPI-12	Wilcoxon sign Rank	*Z* = -2	*P* = .025	.28
Psychosis 1★	Wilcoxon sign Rank	*Z* = -1.13	*P* = .25	.14
*PDQ-39 **	Paired Sample *t* test	*t* = 4.9, 95% *CI*: [7.4,17.4], *df*=60	***P* < .001**	.6
Stigma	Paired Sample *t* test	*t* = 3, 95% *CI*: [.4,2.3], *df*=60	***P* < .003** Corrected α.016	.39
Emotional Wellbeing	Wilcoxon sign Rank	*Z* = -1.5	*P* = .1 Corrected α.016	.19
Cognition	Paired Sample *t* test	*t* = 1, 95% *CI*: [-.2,1.2], *df*=60	*P* = .1 Corrected α.016	.1
EQ-VAS	Paired Sample *t* test	*t* = -1, 95% *CI*: [-.2,1.2], *df*=60	*P*= .06	.2

	Test used	T0-T2 Difference	Sign.	Effect Size !
		***The* α Level: .05, Except of items with ***		
MDS-UPDRS ***	Paired Sample *t* test			
Part I	Paired Sample *t* test	*t* = 2.4, 95% *CI*: [.3,3.3], *df*=60	*P* = .018 Corrected α:.016**	.31
Part II	Paired Sample *t* test	*t* = 4.9, 95% *CI*: [2.6,6.3], *df*=60	***P* < .001** Corrected α:.016	.6
Part IV	Paired Sample *t* test	*t* = 7.8, 95% *CI*: [3.7,6.3], *df*=60	***P* < .001** Corrected α:.016	.9
Total Sleep Hours	Paired Sample *t* test	*t* = -3, 95% *CI*: [1.2,.3], *df*=60	***P* < .001**	.4
UPPS_P ****	Paired Sample *t* test	*t* = -11.3, 95% *CI*: [-49, -34], *df*=60	***P* < .001**	1.4
UPP	Paired Sample *t* test	*t* = -12.3, 95% *CI*: [-40, -29], *df*=60	***P* < .001**	1.5
Negative Urgency	Paired Sample *t* test	*t* = -8, 95% *CI*: [-14, -8], *df*=60	***P* < .001** Corrected α:.01	1.1
Lack of Premeditation	Paired Sample *t* test	*t* = -1, 95% *CI*: [-2.9,.68], *df*=60	*P* = .2 Corrected α:.01	.1
Lack of Perseverance	Paired Sample *t* test	*t* = -3, 95% *CI*: [-2.9, -.7], *df*=60	***P* < .002** Corrected α:.01	.4
Sensation seeking	Paired Sample *t* test	*t* = -4, 95% *CI*: [-8.5, -2.8], *df*=60	***P* < .001** Corrected α:.01	.5
Positive Urgency	Wilcoxon sign Rank	*Z* = 6.6	***P* < .001** Corrected α:.01	.85
ZBI- Carers	Wilcoxon sign Rank	*Z* = -1.1	*P* = .24	.14

✦*One outliner had to be disregarded. ! For T test, the effect size was calculated on the SPSS, however for the Wilcoxon sign rank was calculated in Excel using r = z/√N. *For the PDQ-39 and its subdimensions measured here, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/3) =.0116. ***For the three parts of UPDRS, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/3) =.016. **** For the UPPS-P, UPP and all 5 personality traits, the following formula was applied for α level correction: ($\alpha_{altered}$ =.05/5) =.01.*

3.4.10.8 De Novo Cases of Clinical Depression, Anxiety, Apathy and Anhedonia

Table 44, displays the *de novo* cases of clinical depression, anxiety, apathy and anhedonia. Anxiety showed the lowest, and apathy showed the highest frequency of *de novo* cases at T2.

Table 44 Frequency of De Novo Cases of Clinical Depression, Anxiety, Apathy and Anhedonia

	Depression (PHQ-9 ≥ 9)	**Anxiety (GAD-7≥ 10)**	**Apathy (AES ≥ 38)**	**Anhedonia (SHAPS ≥ 2)**
	N = 61, T2 (6 months post-DBS)			
Number of cases (%)	4 (6%)	1 (1.6%)	43 (70%)	5 (8%)

PHQ-9 = Patient Health Questionnaires – 9 items, GAD-7 = General Anxiety Disorder – 7 items, AES = Apathy Evaluation Scale, SHAPS = Snaith – Hamilton Pleasure Scale.

Summary Points: The T0-T2 Difference in Personality Traits

- Personality traits showed an increase at T2.
- UPPS-S subscales did not respond similarly.

3.4.10.9 The T0-T2 Difference in Personality Traits

In this section, the significance of their T0-T2 differences is presented as shown in *Table 43*. The corrected α levels and p values for the UPPS-P subscales are provided in the same table. The total scores on the UPPS-P and subscores for all personality traits, except lack of premeditation, showed a significant increase, indicating higher impulsivity. In the next step, using Spearman correlation, an analysis was conducted for the correlation between the T0-T2 difference in personality traits the T0-T2 difference in depression, apathy, and anxiety. The corrected α levels were determined as .5/5 = .01. The negative correlation between negative urgency and anxiety remained the same, showing a trend towards a significant level, r (61) = -.235, p = .068. Furthermore, only the lack of perseverance showed a significant weak positive correlation with the difference of apathy (AES), r (61) = .332, p = .009 (corrected α levels = .5/5 = .01). In addition, the T0-T2 difference in both lack of perseverance (r (61) = .317, p =.01) and sensation seeking (r (61) = -.323, p = .011) showed nearly significant weak positive and negative correlation with the difference of anxiety and depression respectively.

Summary Points: Carer Burden at Baseline and T2

- At baseline 96% of carers scored above cutoff point.
- This percentage remarkably reduced to 27%, however, the total score did not significantly reduce.

3.4.10.10 Carer Burden at Baseline

The Zarit Burden Interview, a self-reported scale, measured the carer's burden. A total of 58 carers and their relatives consented to join the study. The relationship between carers and the participants was not specified. Based on the literature, a cutoff point of 17/88 was considered to determine a high burden. As shown in *Table 32*, the frequency of carers scoring above the cutoff point was as high as 96%. In the next step, the Spearman Correlation was used to understand the correlation between participants' psychiatric symptoms and quality of life with carers' burden, *Table 33*. The PDQ-39 and NPI-12 total scores showed a significant moderate and weak positive correlation with the carer's burden on the ZBI. In addition, negative urgency showed a significant weak positive correlation with the carer's burden.

In a separate analysis using Spearman Correlation, the total score on the ZBI was found to have a trend towards a significant very weak positive correlation with age at operation, total LEDD and PD duration. However, the correlation with the latter showed a trend towards a significant level, $r\ (58) = .244$, $p = .06$.

3.4.10.11 The Difference in Carer Burden on the ZBI at T2

The total score of the ZBI at the 6-month follow-up is presented in *Table* 43. However, the total score was non-significantly reduced at T2; the frequency of carers scoring above a cutoff point remarkably reduced from 96% at T0 to 27% at the 6-month follow-up. Further, analyses were conducted using Spearman correlation to determine if the T0-T2 difference in the carer's burden (ZBI) was correlated with the T0-T2 difference of depression, anxiety, and apathy, in addition to the T0-T2 difference of ICDs total and other ICBs. None showed a significant or a trend towards a significant level. No significant or nearly significant results were found for the correlation between the difference in the total score on the ZBI with the difference in the PDQ-39, the UPPS-P and its subscales (Pearson Correlation) and the NPI-12 (Spearman

Correlation). Lastly, for three parts of the UPDRS and total LEDD, as indicative of severity of PD severity, the difference in the carer burden only showed a trend towards a signficant weak positive correlation with part I, r (43) = .346, p = .02, part II, r (43) = .260, p = .02, and part, IV r (43), p = .07, with a corrected α levels of .5/3 = .01.

3.5 Summary Points

1. **Descriptive Statistics at Baseline**

- 69% (n=50) of the participants identified themselves as male,
- 96% (N=70) identified as White British for ethnicity.
- The carers of 58 out of 73 participants consented to join the study

2. **Frequency of Positive Cases of ICBs in Pre-defined Groups at Baseline**

- The frequency of cases scored above the cutoff point (>10) on the QUIP-RS was 26% (n=19).
- The difference of the ICDs total and gambling was negligible between the DA Use subgroups.
- Male participants had a higher frequency of positive cases of the ICDs total (n=23, 32% vs n=23, 13%)
- The frequency for the ICDs total score (n=7, 18.4% vs n=12, 34%) and other ICBs was higher in the late-onset subgroup (n=35).
- The frequency of hobbyism-punding was exceptionally higher in the working subgroup (41% vs 27.3%).
- The users of psychotropics had a higher frequency of positive cases of the ICDs total and all other ICBs except for compulsive gambling and hypersexuality.
- The frequency of positive cases for most ICBs and the ICDs total was higher in the clinically significant anxiety subgroup, the depression subgroup, and apathy.
- Individual ICBs showed a different result than total ICDs.

3. **Correlation of Impulsivity with Personality Traits on the UPPS-P at Baseline**

- The negative urgency was significantly correlated (positive) with compulsive gambling, hobbyism-punding and DDS.

- Lack of perseverance showed a weak positive correlation with hypersexuality and binge eating.
- The only personality traits that showed no significant correlation with either one of the ICBs were lack of premeditation and sensation seeking.

4. Regression Analysis at Baseline

- Impulsivity (ICDs total on the QUIP-RS) at baseline were predicted by Depression.
- Gambling scores were predicted by anhedonia, negative urgency and apathy.
- Hypersexuality scores were predicted by depression and elation.
- Binge eating scores were predicted by anxiety and depression.
- Hobbyism-Punding scores were predicted by depression.
- DDS scores were predicated by anxiety and apathy.
- Multiple ICDs were predicted by cognitive scores and negative urgency.

5. Mood Symptoms at Baseline

- The frequency of clinically significant depression was 53% (n=38).
- Depression showed a significant moderate positive correlation with cognitive subdimension on the PDQ-39.
- The frequency of suicidality (cutoff=1) was 15% at the Baseline.
- The frequency of clinically significant anxiety was 16%.
- Anxiety showed a significant moderate positive correlation with the cognition subdimension on the PDQ-39.

6. Apathy and Pleasure Experiencing Ability at Baseline

- The percentage of patients with clinical apathy was 28%.
- Apathy showed only a significant weak positive correlation with the PDQ-39 cognition subdimension.
- Depression showed a significant moderate positive correlation with anxiety and apathy total scores.
- 34% of the total participants scored above the cutoff for anhedonia.

7. Personality Traits at Baseline

- The Depression scores showed a significant weak positive correlation with negative urgency and positive urgency traits.

- Apathy showed a weak to moderate correlation with lack of perseverance, lack of medication and positive urgency traits.

8. The Frequency of Positive Cases of ICBs Across Pre-defined Groups at T2

- The frequency of positive cases of individual ICBs was reduced.
- The frequency of cases of the ICDs total remained higher in males, late-onset, and below the median LEDD subgroups.
- The frequency of ICDs total positive cases remained higher in retired, non-DA users and psychotropic users.

9. The Frequency of Positive Cases of ICBs Across Pre-defined Groups at T2

- The improvement was statistically significant for hobbyism-punding and hypersexuality.
- The improvement in DDS was followed by compulsive shopping in showing a trend towards a significant level.
- the Improvement in hypersexuality and hobbyism-punding was significantly different only across gender subgroups at the T2.
- The number of cases with multiple ICDs declines significantly at T2.

10. Correlation of Differences in Impulsivity with Other Outcomes at T2

- The improvement in anxiety showed a significant weak positive correlation with the improvement the ICDs total and hypersexuality.
- The worsening in apathy showed a significant weak positive correlation with the improvement in the ICDs total and hypersexuality.
- The PD duration & age did not show a significant correlation with the improvement of the ICDs total.
- The improvement in quality of life was not significantly correlated with the improvement in all measured ICBs.

11. Regression Analysis for Impulsivity at T2

- Improvement in the ICD total was predicted at T2 by baseline anhedonia.
- Improvement in the hypersexuality was predicted at T2 by baseline elation scores.
- Improvement in hobbyism-punding was predicted at T2 by baseline anhedonia.

- Decline in multiple ICDs was predicated at T2 separately by baseline anhedonia and negative urgency (simple linear regression).

12. De Novo Cases of ICBs at T2

- There were 9 cases of *De novo* cases of ICBs
- Hobbyism-punding, binge eating, and DDS were the most frequent *de novo* ICBs, successively.
- No participants had more than 1 *De novo* ICBs
- Depression, cognition and anxiety were worse in *de novo* cases.

13. The T0-T2 Difference in Other Psychiatric and Quality of Life Outcomes at T2

- Quality of life significantly improved
- LEDD significantly reduced.
- Depression did not change significantly.
- Apathy worsened.

14. The T0-T2 Difference in Personality Traits

- Personality traits showed an increase at T2.
- UPPS-S subscales did not respond similarly.

15. Carer Burden at Baseline and T2

- At baseline 96% of carers scored above cutoff point.
- This percentage remarkably reduced to 27%, however, the total score did not significantly reduce.

3.6 Supplementary Materials

Table 45 All Variables Created for the CRISP Study and Utilised in This Thesis.

Variables	**Type of variables**
Demographics	
Age-at-operation	Continuous
Gender	Binary
PD duration	Continuous
Age-at-PD-diagnosis (early vs Late)	Binary
Ethnicity	Categorical
Recruitment time (pre- vs post-operation)	Binary
Carer total number	Continuous
Medications	
Total LEDD	Continuous
Above vs below the LEDD median	Binary
DA Use frequency	Binary
Monoamines Users frequency	Binary
COMB inhibitors user frequency	Binary
Amantadine User frequency	Binary
Anticholinergics User frequency	Binary
Multi-PD medication	Binary
Psychotropics User frequency	Binary
Sleep Pills user frequency	Binary
Pain Killers user frequency	Binary

Variables	**Type of variables**
Impulsive Compulsive Behaviours	
QUIP-RS – Self-rated	
4 ICDs	
ICDs Total scores for 4 ICDs	Continuous
Positive case >CUTOFF = 10	Binary
1- Compulsive Gambling Total	Continuous
Positive case >CUTOFF =7	Binary
2- Hypersexuality Total	Continuous
Positive case >CUTOFF = 8	Binary
3- Binge Eating Total	Continuous
Positive case >CUTOFF = 8	Binary
4- Compulsive shopping Total	Continuous
Positive case >CUTOFF = 7	Binary
Multi ICDs	Ordinal
Other related ICBs	
Hobbysm + Punding total	Continuous
Positive case >CUTOFF = 7	Binary
DDS Total	Continuous
Positive case >CUTOFF = 6	Binary
PICS – RF-rated	
4 ICDs	
ICDs Total scores for 4 ICDs	Continuous

Variables	**Type of variables**
Positive case>CUTOFF = 6	Binary
1- Compulsive Gambling Total	Continuous
Positive case >CUTOFF =4	Binary
2- Hypersexuality Total	Continuous
Positive case >CUTOFF = 2	Binary
3- Binge Eating Total	Continuous
Positive case >CUTOFF = 3	Binary
4- Compulsive shopping Total	Continuous
Positive case >CUTOFF = 3	Binary
Other related ICBs	
Hobbysm + Punding total	Continuous
Positive case >CUTOFF = 7	Binary
DDS Total	Continuous
Positive case >CUTOFF = 6	Binary
Other Psychiatric symptoms	
Depression	
PHQ-9 – Self-rated	
PHQ-9 Total score	Continuous
Clinically significant Depression >CUTOFF = 9	Binary
Suicidality >CUTOFF = 1	Continuous
Suicidality severity	Ordinal Categorical
Anxiety	

Variables	**Type of variables**
GAD-7 – RF-rated	
GAD-7	Continuous
Clinically significant Anxiety >CUTOFF = 10	Binary
Apathy	
AES –Self-rated	
AES Total score	Continuous
Clinically significant Apathy >CUTOFF = 38	Binary
SHAPS – Self-rated	
SHAPS Total score	Continuous
Clinically significant Depression >CUTOFF = 2	Binary
NPI-12 – RF-rated (informant interview)	
NPI-12 total score	Continuous
Delusion	Continuous
Hallucination	Continuous
Agitation/Aggression	Continuous
Depression/Dysphoria	Continuous
Anxiety	Continuous
Elation/Euphoria	Continuous
Apathy/Indifference	Continuous
Disinhibition	Continuous
Irritability/lability	Continuous
Aberrant Motor Behaviour	Continuous

Variables	**Type of variables**
Sleep	Continuous
Appetite and Eating Changes	Continuous
Measures of Quality of Life	
PDQ-39 – Self-rated	
PDQ-39 summary index	Continuous
Mobility (1-10)	Continuous
Activities of Daily Life (11-16)	Continuous
Emotional Wellbeing (17-22)	Continuous
Stigma (23-26)	Continuous
Social support (27-29)	Continuous
Cognition (30-33)	Continuous
Communication (34-36)	Continuous
Bodily Pain (37-39)	Continuous
EQ-5D-5L (patient) – Self-rated	
EQ-VAS (Percentage)	Continuous
UPDRS, I – self-rated & RF-Rated	
UPDRS, I Total score	Continuous
Cognitive Impairment	Categorical
Hallucination and psychosis	Categorical
Depressed mood	Categorical
Anxious mood	Categorical
Apathy	Categorical

Variables	**Type of variables**
Features of DDS	Categorical
Sleep problems	Categorical
Daytime sleepiness	Categorical
Pain and other sensations	Categorical
Urinary Problems	Categorical
Constipation problems	Categorical
Lightheadedness on standing	Categorical
Fatigability	Categorical
UPDRS, II – Self-rated	
UPDRS, II Total score	Continuous
Speech	Categorical
Saliva and Drooling	Categorical
Chewing and Swallowing	Categorical
Eating task	Categorical
Dressing	Categorical
Hygiene	Categorical
Handwriting	Categorical
Doing Hobbies and activities	Categorical
Turning in bed	Categorical
Tremor	Categorical
Getting out of bed or car or chair	Categorical
Walking and Balance	Categorical

Variables	**Type of variables**
Freezing	Categorical
UPDRS, IV – RF-rated	
UPDRS, IV total score	Continuous
Frequency of Dyskinesias	Categorical
Impact of Dyskinesia	Categorical
Frequency of Off time	Categorical
Impact of Off time	Categorical
Complexity of Off time	Categorical
Dystonia	Categorical
Work and Social Life	
WSAS – Self-rated	
WSAS total score	Continuous
Clinically significant work and social impairment >CUTOFF = 15	Binary
Retired/Not Working	Binary
Personality Traits	
UPPS-P – Self-rated	
UPPS-P total score	Continuous
UPP score	
Lack of Urgency	Continuous
Lack of Premeditation	Continuous
Lack of Perseverance	Continuous
Sensation Seeking	Continuous

Variables	**Type of variables**
Positive Urgency	Continuous
Carers' Burden	
EQ-5D-5L (Carer) – Self-rated	
EQ-VAS (Percentage)	Continuous
ZBI– Self-rated	
ZBI care) total score	Continuous
Clinically significant burden >CUTOFF = 17	Binary

Table 46 List of Variables Created for The Comparison of the Retrospective Cohort and the CRIPS Study Cohort

Variable	**Type of variable**
Gender	Binary
Age at operation	Continuous
Age at diagnosis	Continuous
PD duration	Continuous
Pre-operation assessment duration	Continuous
Postoperation assessment duration	Continuous
Family History for Psychiatric Disorders	Binary
Pre-operation History of ICBs	Ordinal
Pre-operation History of depression	Binary
Pre-operation History of Psychosis	Binary
Postoperation ICBs	Binary
Postoperation Depression	Binary

Postoperation psychosis	Binary
Medication reduction after the operation	Binary

Table 47 Variables Utilised in Regression Models

Variables
Age at operation
Age at diagnosis
PD duration
Total LEDD
DA total
Psychotropics total
Anxiety (GAD-7)
NPI-12, Elation
UPDRS, IV
Depression (PHQ-9)
PDQ-9, Cognition
Apathy (AES)
Ability to experience pleasure (SHAPS)
UPPS-P total
UPPS-P, Lack of urgency
UPPS-P, Lack of perseverance
UPPS-P, sensation seeking
UPPS-P, Positive urgency

Chapter 4: Retrospective Evaluation of Neuropsychiatric Clinical Notes Before and After STN-DBS in Parkinson's Disease: A Single Site Audit

4.1 Background and Rationale

King's College Hospital (KCH) is one of the participating centres in the ongoing multicentre observational study – the CRISP study. The CRISP study is a prospective study; its main objective is to assess the effect of DBS on ICDs and other psychiatric symptoms in patients with PD. One of the strengths of the CRISP study is the structured use of a unified set of self-rated scales and semi-structured interviews across all participating centres to fulfil the main objective. As discussed above, these observations will add valuable data to answer an important question. However, a retrospective audit of real-world clinical notes can add one more standpoint to my study of DBS effects on the psychiatric profile of PD patients. This is hoped to measure the effectiveness of healthcare against agreed and proven standards for high quality, and taking action to bring practice in line with these principles so as to advance the quality of care and health outcomes. Specifically, it compares the screening process in the everyday practice neuropsychiatric pre-DBS assessment and the CIRSP study, where assessments are completed using a set of self-rating scales and semi-structured interviews. Although the CRISP study is a research project, it was designed to add the minimum burden on participants and the staff. Comparing it to the common practice can only enhance it without adding any burden. To illustrate, the scales used to screen for psychiatric symptoms are brief, simple, and typically completed within a few minutes. This comparison will show whether they are more efficient in screening for psychiatric symptoms.

Given that face-to-face neuropsychiatric pre-DBS assessment is too critical to be compared to using many self-reported questionnaires, the comparison can only suggest the addition of many scales used in the CRIPS study to the common practice neuropsychiatric pre-DBS assessment. By comparing, the screening process can be enhanced, and patients at risk of

psychiatric complications following the DBS operation can be identified. This addition will reduce the time required for a pre-DBS assessment and enhance the assessment's quality.

Furthermore, several psychiatric symptoms following DBS in PD are known to have pre-DBS risk factors (Houeto et al., 2002; Tir et al., 2007). For example, problematic impulsive behaviours after DBS are thought to be related to preoperative undetected and unreported impulsive behaviours. In addition, specific expected debilitating outcomes after DBS, such as apathy, are shown to be more common in patients with higher self-rated depression scores at baseline (Denheyer et al., 2009). Even the response of motor symptoms to DBS is shown to be correlated to pre-DBS psychiatric symptoms, like depression and anxiety (Sarno et al., 2019).

The comparison will allow us to inform routine clinical practice in pre-DBS neuropsychiatric assessment. As per the current CRISP protocol, we report details of any detected psychiatric symptoms to treating clinicians. We hypothesise that, during the routine pre-DBS assessment, a significant proportion of psychiatric symptoms may remain undetected. A retrospective review of clinical notes for patients assessed on the DBS pathway is conducted, and the prevalence of psychiatric symptoms is compared to the data collected in the CRISP study. Furthermore, this analysis will demonstrate the importance of having all UK DBS centres share a research database. Due to its proximity to the Institute of Psychiatry, Psychology & Neuroscience (IOPPN), KCH was chosen for this single-site retrospective clinical note review. Participants from the CRISP study with the same male/female ratio are selected equal to the number of patients for whom data has been extracted. The review scale is originally larger and includes information about the DBS parameters. However, since DBS parameters are not yet available for the CRISP study, they will not be included in this thesis. A complete comparison will be repeated once the CRISP study is completed, and all DBS parameter-related information is collected.

4.2 Objectives:

I. Description of demographic data and psychiatric symptoms in the cohort of PD patients undergoing DBS surgery at KCH, in comparison with the CRISP cohort
II. The quality of the screening process compared to that in the CRISP cohort

4.3 Methodology

Permission to access medical records was obtained by issuing the RF with a research passport from the King's College Hospital (KCH) R&D office. Ethical approval for this audit was granted with an amendment applied for the CRISP study (See *Appendix* 10). The protocol of current audit follows the health quality improvement partnership (HQIP) guides to reporting and recording. Thus, the staff at KCH including the neuropsychiatrist, neurologist and PD nurses were notified and consulted in developing, planning and documenting records. They have also been notified of evidence of potential impact of action plan resulted from the audit. No publications have yet arisen from this retrospective study. All information regarding data management, archiving, indemnity arrangement, and intellectual property is the same as for the CRISP study. No funding was required to complete the retrospective review—the following subsections present details of the methodology and statistical analysis plan.

4.3.1 Data Source and Sample

A thorough search was conducted for the KCH DBS database to find neuropsychiatric clinical notes for all PD patients who had undergone the DBS operation from January 2015 until December 2021. For all eligible subjects, at least one pre- and one post-operative neuropsychiatric clinical letter or note was reviewed. All extracted data were anonymised and transferred into a password-protected Excel sheet. The extracted data for demographic data and psychiatric records was transformed into variables in an SPSS file, as listed in *Table 46*. All information regarding psychiatric symptoms was extracted from the notes of the same consultant neuropsychiatrist, P.S., who conducts all pre- and post-neuropsychiatric assessments in KCH. All DBS operations were checked in the database for the period in question. The following steps illustrate the process of data extraction:

1- Using a filter, only PD-DBS cases undergoing the operation from Jan 2015 until Dec 2021 were screened on the KCH DBS registry.
2- Subjects selected in the first step on the KCH neurosurgery database were reviewed, and those with one pre- and one post-operation assessment were selected. The last pre-operation assessment was reviewed. As for the post-operative assessment, the first postoperative assessment was reviewed.
3- A comprehensive data extraction was conducted for eligible subjects for variables listed in *Table 46*.

4- Despite extracting more data regarding motor symptoms, medications, and DBS parameters, only 12 variables were chosen to be used in the current data analysis to achieve the objectives of the retrospective review in this thesis.
5- In this thesis, patients who had undergone GPi-DBS were excluded.

4.3.2 Policies and Strategies in the Data Extraction Process

1- Demographics were extracted from reviewed clinical notes, including the database page for the patient, neurosurgeon, neurologist, or PD nurses' clinical letters.
2- When a clinical note did not mention a symptom like "depression", it was coded in the database as "no depression" for that subject. This was done based on the assumption that the assessor has considered the patient's answer "no problem with mood" as "no depression". When it was clinically documented that a patient was on medication for a symptom like depression, this was coded as "yes depression". The notes did not routinely include an assessment of the severity of symptoms, so this was not recorded for review.
3- After all necessary information was extracted into a password-protected Excel spreadsheet,
4- The notes of neurosurgeons, neurologists and PD nurses were reviewed to complete other variables such as "medication reduction after operation" or to extract the operation date for calculation of age-at-operation.
5- Once all data was extracted, the data was anonymised, and the original password-protected Excel file was handled according to the same policies applied to the CRISP study.

The exact number of participants with the same male-to-female ratio and in the same PD duration range was chosen from the CRISP Study to compare the outcomes of the pre-and post-DBS neuropsychiatric assessment at KCH to the outcomes of the CRISP study. The matching process was completed manually on SPSS. To illustrate, the same proportion of males and females as in the retrospective cohort was selected for the comparison. In addition, participants with completed baseline and 6-month follow-ups were prioritised. The same variables were created in the comparison SPSS file where matched subjects from the CRISP study and the retrospective review were divided by an identifier variable.

The available data for certain variables was transferred to the comparison SPSS file. New variables were generated for the matched CRISP study participants to compare them to those in the retrospective review if required. For example, the above cutoff >9 on PHQ-9 was

considered as "yes depression", and below the cutoff was recorded as "no depression". The same was applied to create an equivalent variable for psychosis and ICBs using the psychosis subscales on the NPI-12 (items 1 and 2) and the cutoff point >10 on the QUIP-RS total score, respectively. *Table 46* in the supplementary section *3.5.* provides the list of variables utilised.

4.4 Eligibility Criteria

Inclusion Criteria

1- STN-DBS for PD
2- At least one neuropsychiatric assessment report before and after the operation

Exclusion Criteria

- Nil

4.5 Statistical Analysis Plan

Using the IBM SPSS statistics software (version: 29.0.1.9 [171]), a descriptive data analysis was run for the demographics and other outcomes before the operation. The difference between baseline and postoperative data across the CRISP study and the retrospective variable was tested using the Pearson Chi-Squared test. *Table 48* displays the research questions addressed in the analysis. G*Power software was used to calculate the power for the Pearson Chi-squared. A significant *P* value was defined as one with a value of .05.

Table 48 Research Questions for the Retrospective Review

Variables	Research Questions
Gender	The different frequency of positive cases across the two groups is not associated with gender
Early onset	The frequency of positive cases across the two groups is not associated with PD Onset
ICBs	The frequency of positive cases of ICB is higher in the CRISP Group
Depression	The frequency of positive cases of Depression is higher in the CRISP Group

Variables	Research Questions
Psychosis	The frequency of positive cases of Psychosis is not higher in the CRISP Group
LEDD reduction	The reduction in LEDD is not different between the two cohorts

4.6 Findings

4.6.1 Descriptive Data Analysis

A descriptive statistic is presented in *Table 49*. As shown in the table, the total number in each cohort, in addition to gender proportion and PD duration, is the same for both cohorts as they were matched. However, the retrospective cohort showed an older mean at operation. The two cohorts were also comparable for age at diagnosis. As for PD onset, the retrospective cohort showed a higher percentage of patients with late-onset (>50) than the CRISP cohort. G*Power software was used to calculate the power for the Pearson Chi-squared test at.68.

Table 49 Demographic Characteristics for Each Cohort – Retrospective Review

	Retrospective cohort	**The CRISP study cohort**
N=	33	33
Age at operation Mean (std. Deviation)	70 (6.8)	64 (4.8)
Age at diagnosis Mean (std. Deviation)	54 (5.8)	53 (7.3)
Disease duration Mean (std. Deviation)	15 (3.8)	10 (4.2)
Gender		
♂ *(%)*	21 (63%)	21 (63%)
♀ *(%)*	12 (36%)	12 (36%)
PD onset		
Early-onset (%)	6 (18%)	14 (42%)
Late-onset (%) ∇	27 (87%)	19 (57%)

4.6.2 The Difference in Frequency of Psychiatric Symptoms Across Gender and PD Onset

The Pearson chi-squared test was used to compare the frequency of measured psychiatric symptoms across gender (male and female) and PD onset (early-and late-onset) in the combined cohorts (the retrospective and CRISP cohort). The frequency of ICDs was not different across gender before, X^2 (1, N = 66) = .844, p = *.358* and after the operation, X^2 (1, N = 66) = 2.49, p = *.117.* Similarly, the frequency of depression before, X^2 (1, N = 66) = .038, p = *.8,* and after the operation, X^2 (1, N = 66) = .012, p = *.9,* did not differ across gender. The difference was also not significant for patients with psychotic symptoms across genders before X^2 (1, N = 66) = .732, p = *.3*, and after the operation, X^2 (1, N = 66) = 1.30, p = *.2.* Furthermore, the frequency of patients with late-onset was significantly higher in the retrospective cohort, X^2 (1, N = 66) = 4.591, p = *.032.* Therefore, it was examined if the frequency of ICDs, depression and psychosis was different across PD onset subgroups in the combined cohort at baseline and after the operation. The frequency of ICDs was not different before, X^2 (1, N = 66) = 3.53, p = .171*,* and after the operation, X^2 (1, N = 66) = .195, p = *.6,* across PD onset subgroups. Moreover, depression showed a trend of higher frequency in the late-onset subgroup before, X^2 (1, N = 66) = 2.787, p = .09*,* but not after the operation, X^2 (1, N = 66) = .009, p = *.9*. Lastly, the frequency of patients with psychotic symptoms was not different before, X^2 (1, N = 66) = .121, p = .7*,* and after the operation, X^2 (1, N = 66) = .272, p = *.6,* across PD onset subgroups.

4.6.3 Difference Between the Frequency of Psychiatric Symptoms Between the Two Cohorts

Table 50 displays results for total outcomes for both cohorts pre-and post-operatively. The frequency of ICDs at baseline was not different across the two cohorts, X^2 (1, N = 66) = 1.048, p <*.306.* However, it showed a trend of higher frequency in the CRISP cohort, X^2 (1, N = 66) = 3.66, p = *.056* after the operation. The frequency of depression cases at baseline was significantly higher in the CRISP cohort, X^2 (1, N = 66) = 15.01, p <*.001.* Although it only showed a trend of a higher frequency in the CRISP cohort after the operation, X^2 (1, N = 66) = 2.970, p =*.08.* In addition, the frequency of cases with psychotic symptoms at baseline was significantly more common in the retrospective cohort, X^2 (1, N = 66) = 5.121, p = *.025.* However, the difference was not significant following the operation, X^2 (1, N = 66) = 1.948, p = .138. Finally, the higher reduction of LEDD after the operation in the CRISP cohort was significant, X^2 (1, N = 66) = 3.88, p = *.049*.

Table 50 Results for All Outcomes for Each Cohort - Retrospective Review

	Retrospective cohort	**The CRISP study cohort**
N=	33	33
Pre-operative assessment (months)	12 (6.5)	1
Post-operative assessment (months)	(13)	6
Family History of psychiatric disease	8 (24%)	N/A
Pre-operative ICDs (%)	5 (15%)	10 (30%)
Post-operative ICDs (%)	3 (9%)	9 (27%)
Pre-operative Depression (%)	4 (12%)	19 (57%)
Post-operative Depression (%)	5 (15%)	11 (33%)
Pre-operative Psychotic symptoms	7 (21%)	1 (3%)
Post-operative Psychotic symptoms	4 (12%)	1 (3%)
Post-operative LEDD reduction	21 (63%)	28 (84%)

4.7 Key Findings (Summary Points)

- Patients with Parkinson's are being offered the DBS surgery earlier in its course.
- Patients with psychotic symptoms will benefit a face to face interview in clinic.
- Compared to the CRISP cohort, the retrospective cohort reported less psychiatric symptoms.
- The post-DBS assessments period in the retrospective cohort were remarkably longer than the CRISP study.

4.8 Action Plan

- Addition of brief scales to pre- and post-DBS will increase the screening quality.
- This action is SMART in being **S**pecific about involved area, **M**easurable by validated scales, **A**chievable due to the fact that all recommended scales are brief and

simple to understand and **R**ealistic as it is managed in a specific **T**ime frame before and after the DBS.

4.9 Recommendations

- The burden should be kept minimum on both patients and staff.
- Since the pre-DBS face to face psychiatric assessment will be sufficient to detect severe and unstable psychiatric patients, scheduling the completion of added scales after an operation date is confirmed will increase the openness of eligible patients when reporting psychiatric symptoms, including impulsivity. This is because patients are assured of receiving the DBS therapy.
- This set of scales can be sent by mail or email automatically or handed to patients in clinic so that the assessment period is not as long as the retrospective cohort. Also, any problematic psychiatric symptom will be detected earlier.

4.10 Presentation

The main results of the audit are discussed in internal multidisciplinary meetings and at the annual UK DBS network meeting.

4.11 Caveats of the Audit

1. The data collected in the single site audit were recorded mainly "yes" or "no", as noted in the clinical letters, whereas corresponding variables in the CRISP cohorts were created based on being above well-studied cutoff points on a validated scale. This disparity may have influenced the quality of the assessment, given the effects of rating agencies and the tendency to conceal or underreport symptoms in pre-DBS assessment. However, the retrospective review outcomes have already influenced the pre-DBS assessment routine at KCH by suggesting the use of validated scales for major psychiatric symptoms, such as anxiety, depression and apathy.

2. The clinical letters of more than one assessor, including neurologist, neurosurgeon, PD nurse and neuropsychiatrist, had to be reviewed to complete the review for some cases.
3. The assessment periods before and after the operation significantly differ between the two compared cohorts, which might have influenced the outcomes. This limitation could be addressed in future by scheduling posts or emails that with validated self-rated questionnaires. These could then also provide valuable information for the subsequent face-to-face assessment.

Chapter 5: Discussion

In this chapter, the results of baseline and 6-month follow-up are discussed. First, the baseline characters and their relevance in the CRISP study and DBS-PD studies will be discussed. Then, PD-related medications at baseline and the 6-month follow-up are discussed. Next, ICBs are discussed in detail at baseline separately before covering changes in ICBs after the STN-DBS subsequently. The discussion on other psychiatric outcomes follows a brief comparison between ICBs outcomes on the QUIP-RS and PICS. Lastly, the outcomes for carers' burden are discussed from the CRISP study. In the last sections, the clinical implications of the retrospective review in the single site audit, limitations, future direction in observational studies and a brief discussion of the effect of the COVID-19 pandemic halt are discussed.

Generally, whether it is a genetic or environmental factor, the manifestation and progression of PD take an extremely heterogeneous trajectory. As a result, psychiatric symptoms may manifest themselves in various ways. In addition, cultural and social factors make assessments of psychiatric symptoms more challenging in clinical and research settings. To illustrate, this feature becomes more problematic in research when there is a lack of disease-specific measuring tools, unity in their utilisation and inclusive cohorts. The Orion MedTech database established during the current project will help UK DBS centres have unified research using the same tools and larger inclusive cohorts.

5.1 Baseline Characteristics of the CRISP Study Cohort

The mean age (SD) of the participants who were recruited (baseline) and who completed the 6-month postoperative follow-up (T2) was 62 (7), ranging from 42-76. The relevance of age will be discussed in general and then in the face of individual outcomes later in the chapter. Of the 73 patients recruited at baseline (T0), one patient passed away at age 58 (1.3%) due to intracranial haemorrhage weeks after completing the 6-month follow-up. Another participant, 66, developed an infection following the operation, resulting in the electrodes being removed. The cause of the death in the deceased participant was unlikely to be surgery-related, given the age of the participant and the time between surgery and death. Although age may be associated with immediate postoperative complications like confusion (Abulseoud et al., 2016) or

worsening in certain psychiatric symptoms like apathy (Kirsch-Darrow et al., 2011), owing to the advancements made in the procedure, it is relatively safe.

Furthermore, intracranial haemorrhage caused by electrode implantation, reported to be as low as 0.5-5%, results in immediate symptoms intraoperatively or within minutes to hours following the operation (Jung et al., 2022). As for infection, it is reported to be the most common intraoperative complication at 5%, resulting in device and electrode removal (Jung et al., 2022; Tabaja et al., 2023). However, the surgery failure and electrode removal rate was reported to be much higher in a retrospective study of multiple North America databases (N=28000) at 15-34% (Rolston et al., 2016). It is not, however, an age-related complication.

The current cohort is relatively older than the cohort of a Korean nationwide study about the mortality in PD patients after DBS, with a mean age (SD) of 60 (9) (N=1079). The authors identified age 70s and 60s to be associated with a higher death rate following the operation compared to age 50s and < 50s with Hazard Ratios of 3 and 2.4 *vs*. 1.4 and 1, respectively (Kim et al., 2023). During their over 10-year follow-up period, the mean time (SD) to death following the DBS implantation was reported to be 10 years (2.8). Furthermore, a clinical trial (STN-DBS n=60 and GPi-DBS=61 *vs* best medical treatment n=134) which studied an STN-DBS cohort with a similar mean (SD) age to the CRISP study's cohort, 62 (8.4), reported that the improvement in the quality of life and rate of adverse events was similar in younger (< 70) and older patients for both groups 6 months after the operation (Weaver et al., 2009).

Consistently, a case-control study of 104 patients with a mean (SD) age of 77 (2.8) *vs* 60.8 (7.1) reported that patients above 75 had a similar DBS effect on motor and psychiatric symptoms 1 year after the operation(Mitchell et al., 2020). According to a meta-analysis of 48 studies, including 1768 patients, the mean age and PD duration are highly heterogeneous across STN-DBS studies (Bucur & Papagno, 2023). Therefore, age cannot be a reliable predictor for postoperative surgery failure or fatal complications partly due to lack of evidence or age heterogeneity across studies. As a result, an evidence-based review by a group of experts recommends that patients with advanced PD should be considered for STN-DBS even with an age-related cognitive deficit, as it can improve motor symptoms, reduce the complications related to Parkinson's medications and improve mild to moderate depression and anxiety (Volkmann et al., 2013).

The mean PD duration (SD) in those participants who recruited and completed the 6-month follow-up was 10 (4), ranging from 4-20. This is shorter than the average PD duration reported

in other studies 13-14 (Desouza et al., 2013; Groiss et al., 2009; Westerink et al., 2023; Zahodne et al., 2009). The duration of the PD is not specified in many studies (Schadt et al., 2006; Volkmann et al., 2001; Westbay et al., 2015). The association between PD duration and main outcomes are discussed further in this chapter. As for its relevance, there is an ongoing discussion about whether PD patients should undergo DBS operation earlier to increase their quality of life and to avoid their cognitive impairment becoming a reason for their ineligibility for DBS therapy at advanced stages. Advocates of this argument believe it is important to start stimulating early because more dopaminergic neurons are available. It is reported that half of the dopaminergic neurons in the substantia *nigra* are still available at early stages (Schapira & Obeso, 2006).

Hence, it is argued that DBS must be considered as soon as medical treatments' motor and non-motor complications become problematic. Commencing medical therapy as soon as the diagnosis is made is also gaining support (Chen & Swope, 2007; Hauser, 2010; Schapira & Obeso, 2006). Nevertheless, in a retrospective study of a large cohort including UK PD patients (N=7775), the authors reported that 68% and 16% of the UK PD patients were on monotherapy and polytherapy, respectively, with levodopa, pramipexole, levodopa-entacapone combination and ropinirole being the most prescribed monotherapy at 29%, 20%, 17% and 14%, respectively (Kalilani et al., 2019). Considering the concerns regarding the psychiatric complications of dopaminergic agents (Cummings, 1991; Wolfschlag & Håkansson, 2023), as well as their already-known motor complications (Schuepbach et al., 2013), it is worth discussing alternative surgical treatments at earlier stages as well. However, recent studies have reported that the most prescribed medication, levodopa, has the least association with psychosis when compared to the risk of age, PD duration and observable changes in the brain (Ecker et al., 2009).

In addition, other drug-induced psychiatric symptoms are reportedly manageable by reducing the dose, switching drugs, or adding psychotropic agents (Abosch et al., 2011; Kuzuhara, 2001). That said, the motor complications and resistant symptoms dictate the discussion to be taken seriously. Indeed, in a clinical trial (EARLYSTIM), PD patients with early motor complication, mean PD duration of 7.5 and mean age (SD) of 52 (6) were divided between an STN-DBS and medical treatment group and medical treatment alone group (n=124 *vs.* n=127). The authors reported that after two years, the DBS-STN showed a superior improvement in quality of life and motor symptoms and fewer adverse psychiatric events, such as impulsivity and mood symptoms (Schuepbach et al., 2013). The authors reported that experts approved the

standard of medical therapy, and blinding was applied to the motor scores while reviewing the recorded videos. Another important point in considering DBS earlier is preserving working capability in PD patients. It was shown in a retrospective study (N=40) that 16 out of 18 actively working (5 days a week) patients were able to preserve their capability to work for up to two years, and only 1 of the 18 patients stopped working due to PD-related disabilities after the DBS operation (Deli et al., 2015).

This, however, has not been reported in studies with longer follow-up periods. Despite such positive results, a few critical points must be established to reach a consensus. The first point is whether DBS can modify PD, i.e., slow down or accelerate the disease's progression. Several non-human studies have suggested that DBS can slow down the disease; however, such studies use animal PD models that differ from the PD in human subjects in many ways, such as different progression courses (Dauer & Przedborski, 2003). Although the animal model of PD shows some promising results after DBS in protecting the remaining dopaminergic neurons, human studies report conflicting results. The washout period for the stimulation effects is the main limitation in human studies that showed promising results (Emamikhah et al., 2022). In addition, the long-term follow-ups in PD patients with DBS do not report that DBS prevents or reduces the severity of inevitable disabling symptoms of advanced stages of PD, including psychiatric disorders and cognitive impairment (Kenney et al., 2007; Kim et al., 2014; Rizzone et al., 2014; Volkmann et al., 2004).

For example, a case-control study (n=33 in each group) study, using F-fluorodeoxyglucose positron emission tomography (FDG-PET) reported that metabolic changes in basal ganglia, which were correlated with motor improvement on the UPDRS at 3rd month postoperatively, were not stable at the 12th month (Ge et al., 2020). This leads us to the second point: whether the disease-modulating effects of DBS in PD can reach beyond the dopamine network to improve the non-motor symptoms. According to a systematic review, including 29 studies of STN-DBS effects on brain metabolism and blood flow, DBS increased metabolism is not confined to the striatum, but is also observed in the limbic region and frontal lobes (Kokkonen et al., 2022). The third point is the safety profile of the invasive surgery and the economic justification in the face of available alternative medications. The third point is the main argument on the opposing side of the DBS use in the early stages. Nevertheless, in patients currently being selected for DBS, the first main objective is the symptomatic relief of motor symptoms, and the second is to improve the quality of life and the carer's burden. If the outcome is more years of quality of life for patients and carers, the argument should be settled in favour

of earlier consideration of the DBS. The search to optimise DBS parameters to reduce negative side effects should remain active.

Before discussing the last characteristic, gender differences need to be addressed. The percentage of male participants recruited at baseline (N=73) was 69% (n=50), compared to 72% (n=44) of those who completed the 6-month follow-up (N=61). The gender differences in the context of individual outcomes will be discussed later, it is essential to highlight the significance of equal representation of both genders. In our study, the mean age (SD) for females was 63 (5.8), whereas for males, the mean age was 61 (7). In female participants, there was only one participant below 50, whereas in the male group, there were four participants aged below 50.

The fact that the risk of developing PD is double in males cannot explain the gap between the two genders in the PD-DBS studies (Cerri et al., 2019). The disease-related mortality is significantly higher, and the progression is faster in females (Setiawan et al., 2006). The age issue will arise again when female participation in PD-DBS studies is discussed. Motor symptoms can develop later in the course of the disease in female patients than in male counterparts (Baba et al., 2005). Therefore, they may require DBS surgery at a later age. In addition, motor complications such as dyskinesia are also significantly higher in females (Accolla et al., 2007; Colombo et al., 2015). According to a recent nationwide inpatient sample analysis conducted in the USA, female gender was a negative predictor for DBS utilization in PD and essential tremor (Sarica et al., 2023). The difference in male-to-female participation in DBS studies has been observed in other relevant studies (Krause et al., 2022; Kübler et al., 2023). This is despite the lack of evidence for females to experience less benefit and the numerous reports that indicate the opposite (Accolla et al., 2007; Chandran et al., 2014; G. M. Hariz et al., 2013; Kübler et al., 2023). Discussing the reasons for such disparity is beyond the scope of this thesis; however, it has been suggested that it may be either a sociocultural-related matter (Mazure & Jones, 2015), personal preferences (Setiawan et al., 2006), or clinician bias in referring patients (Jost et al., 2022).

Regarding personal preferences, which may be affected by stigma and social support, female participants in the CRISP study scored higher than males on measures of PD-specific health related quality (PDQ-39) at baseline. This is consistent with the findings of another prospective study (Male n=31, Female n=18)(G. M. Hariz et al., 2013). Moreover, 2 out of 80 patients who informed us they had refused the DBS operation were of female gender. The reason for DBS rejection in females was reported in a longitudinal cohort study (male n = 214, female n= 101)

to be mainly depression, which was significantly different from that in males (Jost et al., 2022). The authors stated that the rejection was decided jointly by a multidisciplinary clinical team and patients. In the CRISP study, the frequency of clinical depression was not significantly different across genders at baseline (56% vs 48%). However, this will be best observed at the end of the one-year follow-up, as planned in the CRISP study.

At baseline, 96% of participants identified as white British, while at 6 month follow-up, 97% did. The inclusion of minority ethnicities in research has been a hot topic as the general population is becoming more diverse in terms of ethnicity, especially in Western, developed countries like the UK. As a result, it is necessary to promote the inclusion of minorities in all research that may impact the services being delivered to the public, like the NHS. The surge in patients from ethnic minorities who receive the service is particularly significant (Ejiogu et al., 2011).

Therefore, their inclusion in research will improve outcomes and efficiency. The current low rate of ethnic minority inclusion may be due to the socioeconomic differences, language barriers and understanding of research (Ejiogu et al., 2011; Gill et al., 2013). Others reported in a nationwide study that despite representing 7% of PD cases in the USA, African Americans make up only 1.8% of patients who undergo the operation (Sarica et al., 2023). The authors have suggested a lower referral rate and medical conditions that are believed to be associated with more complications as potential reasons. Although this is beyond the scope of this thesis, it is relevant to emphasise that among patients contacted by the research team, 4 out of 7 who declined to enter the study or dropped out before the 2nd follow-up were of ethnic minorities. As per the protocol, the reason for study rejection was not inquired about. In future studies it will be essential for researchers using public services to provide as much information as possible to inform the relevant ongoing debates.

5.2 Medications

All participants were prescribed Levodopa preparations at baseline, see *Table 21*. Frequencies for other medications were as follows: DAs (53%), MAO-Bs (49%), COMT inhibitors (23%), Amantadine (26%), anticholinergics (3), psychotropics (31%), analgesics (painkillers; 12%) and sleep medications (12%). Here, a brief comparison will be made between the medications in the CRISP study and the main studies discussed further in this chapter. The total LEDD

mean (SD) of 1182 (591) in the cohort was only comparable to the secondary analysis of the PREDI-STIM study (Santin et al., 2021). It was higher than a retrospective study (N=89, the mean [SD] of total LEDD= 894 [504]) (Kim et al., 2013), a prospective cohort study (N=26, 824 [479]) (Janssen et al., 2014) and a consecutive case series (N=150, 299 [254]) (Merola et al., 2017), but lower than another retrospective study (N=598, 1395 [342]) (Ardouin et al., 2006), a consecutive case series (N=172, 1364 [368]) (Merola et al., 2017), and two prospective and retrospective studies (N=110, 1236 [490] (Eusebio et al., 2013), (N=69, 1288 [471] (Abbes et al., 2018) and consecutive case series (N=37, 1238 [128]) (P. Rossi et al., 2017). As seen, there is heterogeneity in baseline LEDD across studies with different study designs, which indicates the severity variation or variation in prescribing practices at baseline. The relevance of baseline total LEDD with individual outcomes is discussed in the next section.

Furthermore, in the CRISP Study, only 31% (n=23) of participants were receiving psychotropic medications, including antidepressants (27%, n=19), mood stabilisers, sleep medications and anxiolytics. In the face of the high frequency of clinically significant cases of depression and anxiety, which will be discussed further, the frequency of psychotropic prescriptions can be considered low. Although there is a lack of consensus on using antidepressants for PD depression (Weintraub, 2020), the efficacy of the Serotonin Selective Reuptake Inhibitors (SSRI) *versus* placebo is convincing in a meta-analysis (Skapinakis et al., 2010). In addition, in a *post hoc* analysis of the ADAGIO study, the use of a combination of antidepressants with certain PD medications, such as rasagiline, is shown to be well tolerated and effective in managing depression in the early stages of PD (Smith et al., 2015). Citalopram and sertraline are reportedly safe at the smallest therapeutic dose when co-administered with 1 mg of rasagiline, despite the common concern regarding serotonin syndrome (Aboukarr & Giudice, 2018; Panisset et al., 2014). Moreover, certain PD medication classes are shown to have arguable antidepressant effects due to their mechanism of action, such as monoamine oxidase (Frenklach, 2016). Careful consideration of the antidepressant effect when prescribing PD medications could help reduce depression. However, there are other effective non-pharmacological treatments for depression, such as CBT (Dobkin et al., 2011) and exercise (P. L. Wu et al., 2017). In the current cohort, no information is collected regarding such alternative treatments. Therefore, the cause of the seemingly underprescription of psychotropics remains unknown.

The total LEDD significantly reduced 6 months postoperatively, see *Table 43*. This is in line with serval studies that have reported a significant reduction of total LEDD starting from the

early months following the DBS activation (Deogaonkar et al., 2011; Follett et al., 2010; Houvenaghel et al., 2016; Okun, 2012; Schadt et al., 2006; Somaa, 2021). The frequency of usage of all classes of medications was reduced except for psychotropics. Due to a lack of data on the date of adding psychotropic medications, it is not possible to investigate if their addition is associated with changes in mood symptoms, which will be discussed later. The frequency of subjects taking more than 3 PD medications reduced as well, indicating improvement in motor symptoms.

5.3 Impulsive Behaviours at Baseline

The frequency of positive cases of ICDs and related ICBs was higher in the male group (except compulsive shopping), late-onset PD, the above LEDD median, retired and psychotropic user subgroups, and participants with clinical depression, anxiety and apathy (see *Table* 25-28). However, these differences were only significant for anxiety, depression, and apathy. The association between the ICDs total on the QUIP-RS with psychiatric comorbidities was supported by a significant weak correlation with other psychiatric outcomes such as the ability to experience pleasure or anhedonia (SHAPS) and the non-motor experiences (UPDRS, I). The results for individual ICDs and other related ICBs varied.

5.3.1 Frequency of ICBs at Baseline

In the CRISP study, the frequency of ICDs, including compulsive gambling, hypersexuality and compulsive shopping at the baseline on the QUIP-RS was relatively consistent with what a cross-sectional study (DOMINION) reported in their total non-DBS PD cohort (N=3090) at 5%, 3.5%, 5.7%, respectively (Weintraub et al., 2010). In another recently conducted study of 892 Greek non-DBS PD patients, the authors reported a lower frequency for the three ICDs at 2.9%, 3.9%, and 1.9%, respectively (Kapsomenakis et al., 2023). As for binge eating, the rate in the CRISP study (17.8%, n=13) was much higher than other non-DBS cohorts at 2.8% (Smith et al., 2016), 9% (Kapsomenakis et al., 2023) and 5% (Weintraub et al., 2010). Furthermore, the mean PD duration was reported to be 6 months at baseline in a secondary analysis of The Parkinson Progression Markers Initiative (PPMI), an observational multicentre international study of early diagnosed patients (N=320). The authors reported a lower frequency of binge eating (Smith et al., 2016).

In the analysis of current data, the results for hobbyism and punding were combined, which may be the reason behind its higher frequency of 32%, compared to what others reported at 5% (Smith et al., 2016) and 1.6% (Kapsomenakis et al., 2023). The frequency of DDS was also higher than reported in other non-DBS cohorts, 16.4% (Smith et al., 2016) and 1.2% (Kapsomenakis et al., 2023). It should be noted that the CRISP study's cohort, who have been selected for the DBS, had a longer PD duration, meaning more advanced PD. Both studies above had larger cohorts with remarkably shorter mean PD durations of 5-7 years. Although it indicates a higher frequency of ICDs and related ICBs in DBS candidates, comparing the baseline frequency of the ICDs and related ICBs at baseline to other PD-DBS studies is critical. Therefore, the studies reviewed in *Chapter 2*, the narrative review, will be examined more deeply. This narrows the focus on studies that reported the frequency of ICBs at baseline before the DBS operation. In addition, studying the prevalence of ICBs in DBS candidates is crucial as the disease is heterogeneously progressive and results from non-DBS PD cohorts will not sufficiently inform research discussion about ICBs and their response to STN-DBS.

A secondary study of the multicentre cohort study (PREDI-STIM) (N=217) reported that the frequency of positive cases of ICDs on the Ardouin Scale of Behaviour in Parkinson's Disease (ASBPD) was 10% at baseline. The authors did not detail the individual cases of positive ICDs and related ICBs (Santin et al., 2021). Furthermore, in a secondary analysis of a multicentre, open-label, randomised clinical trial (EARLYSTIM) (STN + medical therapy =123 *vs.* medical therapy n=127), the frequency of positive cases of ICDs (ASBPD) was reported at 0.8% at compulsive gambling, 5.6% for binge eating, 3.2% for hypersexuality, 0.8% for compulsive shopping, and 0.8% for DDS (Lhommée et al., 2018). However, using the same questionnaires, a multicentre, prospective and retrospective study (N=102) reported the frequency of binge eating and hobbyism at 29% and 17%, respectively, in line with the high rate observed in the CRISP study at baseline (Kim et al., 2013).

The lower frequency of ICBs could be attributed to the impulsivity measuring tool and the larger cohort in the former two studies. A comparison between the QUIP-RS and PICS results in the face of the results of others is presented later in this chapter. At various levels of detail, other prospective and retrospective studies have shown that ICBs have heterogeneous frequency rates (Abbes et al., 2018; Ardouin et al., 2006; Eusebio et al., 2013; Gee et al., 2015; Janssen et al., 2014; Kim et al., 2013; Merola et al., 2017; Pallanti et al., 2010; Somma et al., 2022).

5.3.2 Relationship of ICBs with Characters and Other Psychiatric Symptoms at Baseline

The following section covers the correlation analyses discussion on impulsivity with characteristics, medications, and psychiatric outcomes at baseline (see *Table* 28-29). In addition to regression analyses at baseline and 6-month follow-up. These analyses were based on the narrative review results presented in *Chapter 2* and a search for more recently published studies. To discuss the severity of ICDs collectively, the ICDs total will be discussed. The ICD total is the combination of scores for compulsive gambling, hypersexuality, binge eating and compulsive shopping.

5.3.3 Relationship Of ICBs and Age, PD Duration and Medications

The total ICDs scores at baseline showed a significant weak positive correlation with age. As discussed, scores of ICDs were higher in late-onset PD, contrary to the findings of others (Abbes et al., 2018; Janssen et al., 2014). It has been reported in a cross-sectional study that self-reported impulsivity was more associated with younger age at diagnosis and increased with PD duration (Abosch et al., 2011). That said, the authors reported that among their cohort, the DBS group had a longer PD duration and older age compared to the non-DBS PD group, and when this was adjusted for, no significant difference was found for impulsivity. This conflicting result may be due to the cutoff age distinguishing early- and late-onset PD (Mehanna et al., 2022). It can also result from heterogeneity of PD underlying pathology and its progressive course (Dauer & Przedborski, 2003). Nevertheless, a positive correlation with age remains the consistent finding that indicates impulsivity may have resulted from an interaction of premorbid vulnerabilities and PD progressive and extensive pathological neurodegeneration affecting emotional, cognitive and behavioural dysfunction.

Although small cohort studies reported a significant difference in the ICDs (QUIP) between DA users and non-DA users (Rossi et al., 2017), this was not the case in the CRISP study, the secondary analysis of the PREDI-STIM (Santin et al., 2021), and other studies (Kim et al., 2013; Merola et al., 2017; Pallanti et al., 2010). The association between baseline impulsivity and such total LEDD and DA use at baseline is occasionally overlooked in relevant studies (Abbes et al., 2018; Gee et al., 2015). The association of the increase in impulsive behaviours over 3 years after diagnosis with the increase in the accumulative rate of Dopamine

Replacement Therapy (DRT)[24] has been reported in a large cohort study (N=320) (Smith et al., 2016). The DA agents have been shown in experimental studies to be associated with making risky decisions in Beads (N=11) (Lees et al., 2013) and Gambling tasks (N=15) (Lule et al., 2012). However, the secondary analysis of the PPMI reported that the ICD rate was 7% at baseline for patients not on any form of DRT, indicating a pre-DRT risk for developing ICDs (Smith et al., 2016). Nevertheless, it is assumed that problematic DRTs have been adjusted over time; therefore, not finding a significant difference between DA and non-DA users is reasonable in DBS candidates. It simultaneously indicates a complex underlying pathology, which will be discussed further.

Like DA agents, there was no correlation between total LEDD and impulsivity (ICDs and ICBs); however, when the cohort was divided by the median LEDD, a trend indicated higher impulsivity in the below LEDD median subgroup. An exception was the DDS, which was relatively more frequent in the above LEDD median subgroup. Others have observed the association between higher LEDD and DDS. A consecutive case series (STN-DBS N=110) reported that patients with DDS had a significantly higher LEDD and worse motor score during the medication-off period at baseline (Eusebio et al., 2013). However, in the secondary analysis of the DOMINION study, the authors reported no association between the severity of motor symptoms and impulsivity (Weintraub et al., 2010). Given the short PD duration of their cohort, over time, the complexity of this association with individual ICBs can increase. With more progressed dopaminergic degeneration, there can be more need for LEDD to compensate for the deficit of dopamine, which leads to more medication-related side effects. In response to unwanted side effects, like impulsivity, it can be argued that reducing the total LEDD increases the chance of referring PD patients to DBS clinics earlier.

In a subset of PD patients with ICDs, the need for higher LEDD is additionally associated with a lack of adequate dopamine reuptake at axon endings, resulting in amplified physiological activities of dopamine, which may be expressed in the form of addiction-like behaviours (Voon et al., 2014). In 2 studies, the abnormality in striatal dopamine transporter (DAT[25]) availability was associated with ICDs. This change, when present in both hemispheres has been reported

[24] DRT was defined by the authors as levodopa, dopamine agonist, amantadine or monoamine oxidase-B inhibitor.

[25] DAT are proteins located in axons' membrane which act as the main mechanism of removing the dopamine from the synapses and terminate their neurotransmission (Voon et al., 2014).

in mixed ICDs (Voon et al., 2014) and compulsive gambling (Cilia et al., 2010). These studies investigate if the increase in ventral striatal dopamine release observed in PD patients with ICD is caused merely by an increase in dopamine release or if it is due to impaired dopamine uptake resulting from the reduced DATs. An interesting finding for these studies was that the reduced DATs were not significantly different in hobbyism and punders compared to PD patients with no ICDs, indicating a distinct underlying pathology for hobbyism and punding. The LEDD total and the DDS, in particular, are thought to have a more complex relationship with the severity of underlying PD pathology, as reported by multiple neuroimaging studies. Two studies, including animal studies, have found the same results in hypomanic/manic states, which is a common feature of DDS (Cilia et al., 2014). However, these studies had some significant limitations, such as a lack of DAT neuroimaging data for hypomanic/manic patients (Ashok et al., 2017; van Enkhuizen et al., 2014).

It is also believed that there is a premorbid vulnerability to the effects of the DAT changes (Theis et al., 2021). This vulnerability can be acquired through inheritance, as shown in ^{123}I-FP-CIT SPECT and high-resolution PET studies, to be the case in non-PD gamblers (N=15) (Pettorruso et al., 2019) and tobacco and cannabis addicts (N=14) (Leroy et al., 2012). In the former group, the days of gambling over the last month were inversely associated with Ventral striatal DAT availability. Both studies had a small cohort with a similar number in the control group. However, they support a hypothesis for a vulnerability related to the effects of reduction in DAT availability. In PD cases, this vulnerability is thought to be acquired through neurodegeneration. It is believed in the vulnerability-stress model that this vulnerability exists before starting the medications. In a study, PD patients (N=35) were followed up retrospectively two years after they had undergone ^{123}I-FP-CIT SPECT[26] imaging before starting any medications. The authors reported that 11 patients had developed ICDs (QUIP-RS) with a significant negative weak and moderate correlation with the DAT availability in the right ventral striatum and right anterior-dorsal striatum (Vriend, Nordbeck, et al., 2014). The authors also reported that of 11 patients, only eight received DAs. Notably, the mean PD duration in all these studies is significantly shorter than in cohorts undergoing DBS. Therefore, these associations between DA and LEDD with impulsivity can be dose- and duration-related. It can also be related to a specific medication such as pramipexol and ropinirole (Fang et al., 2015; Holman, 2009; Koschel et al., 2022). Furthermore, according to multiple studies

[26] This technique uses ^{123}I-labeled markers that binds to the dopamine transporter (DAT) to visualise them.

functional MRI studies, there is an impairment in frontal-striatal connectivity (N=30)(Ruitenberg et al., 2018) and activation in the anterior cingulate gyrus and frontal orbital cortex (N=5) (Thiel et al., 2003) which result in impaired decision-making in tasks that are reward-expectation based. The baseline results of the CRISP study, and others with similar results discussed above, indicate that a mix of the vulnerability-stress model and underlying pathology of PD, integrating the frontal lobe dysfunctions, is involved in pre-DBS impulsive behaviours.

5.3.4 Relationship Of ICBs and Working and Social Adjustment

It was hypothesised that the frequency of ICBs would be associated with employment status. This was essential to test due to the impact of ICBs on work and social adjustment (Okai et al., 2011). Using the WSAS scale, the frequency of retired participants was 44 out of 73 at baseline. Although the literature does not provide much information on its impact, the difference in frequency was investigated in the CRISP study. The frequency of individual ICBs across retired and working subgroups changed among individual ICBs. Hypersexuality showed the smallest difference, while the hobbyism-punding frequency was much higher in the working group; therefore, it might have a more significant impact on patients' work and social adjustment. Compulsive gambling, binge eating, and DDS were more common in the retired subgroup. While none of the differences above were significant, they can point to the risk that individual ICBs pose to work or social adjustment, or vice versa. Although data on the impact of ICBs on work and social adjustment was not collected. That said, the PICS rates the severity by including the social impact of individual ICBs. The fact that there is a low rate of positive cases on the PICS compared to the higher rate of the QUIP-RS suggests that ICBs are not socially impairing in the CRISP cohort.

Furthermore, working can be considered a protective factor for developing ICBs. As it will be discussed further below, depression was significantly higher in the working subgroup. However, the only ICB higher in the working subgroup was the hobbyism-punding. Other ICBs were more common in the retired subgroup, and the positive cases of ICBs in the retired subgroup also had a significantly higher rate of clinical depression. Moreover, at baseline, examining the interrelation of ICBs on the QUIP-RS produced some insight into the problematic behaviours. Compulsive shopping showed a significant moderate correlation with hobbyism-punding. This may not be a coincidence, given that some hobbyism-punding activities are also related to spending. The current study did not specify the form of hobbyism and punding. However, its significant correlation with compulsive shopping, on the one hand,

and its significantly higher frequency among working groups may suggest financial status as a determinant for the severity of their impact.

5.3.5 Relationship Between ICBs and Gender

The association of individual ICBs with genders reportedly vary at baseline. In line with other studies, the baseline results indicated that the rate of impulsive behaviours is higher among male participants, except for compulsive shopping (Abbes et al., 2018; Kim et al., 2013; Kon et al., 2018; Kübler et al., 2023; Weintraub et al., 2010). However, the difference was statistically significant only for hypersexuality in the CRISP study. Indeed, one of the similarities between the two scales used in the CRISP study (QUIP-RS and PICS) was that they revealed no positive cases of hypersexuality and compulsive gambling in female participants. The baseline difference in frequency of ICBs across gender was overlooked in several studies, including the secondary analysis of PREDI-STIM (Abbes et al., 2018; Gee et al., 2015; Pham et al., 2015; Rossi et al., 2017; Santin et al., 2021). The higher frequency of individual ICBs in males is reported in other studies. A retrospective study (N=598) reported 7 male and 1 female PD patients with compulsive gambling before DBS operation (Ardouin et al., 2006).

Males were also reported to have a higher frequency of DDS (16/18) in a consecutive case series (N= 110) (Eusebio et al., 2013). In a prospective cohort (N=24), there were 5 cases of punders, and three of them were male (Pallanti et al., 2010). These were rare studies as the authors had focused on individual ICBs (compulsive gambling, DDS and punding), and the diagnoses were based on the DSM-IV criteria (DSM-IV-TR for the latter study). Another retrospective study (N=89) found that males dominated the ICB-positive groups prior to the operation, with exceptionally high levels of hypersexuality (Kim et al., 2013). The study of differences in binge eating across genders has produced conflicting outcomes (Weintraub et al., 2010; Zahodne et al., 2011).

Furthermore, compulsive shopping is reported in other studies to be more common in female participants, while male compulsive shoppers were reported to have more psychiatric comorbidities (De Mattos et al., 2016; Granero et al., 2016; Weinstein & Dannon, 2015). However, most studies have mainly included female participants who are seeking treatment. Similarly, the predominant male participants in individual ICB cases can be due to the higher number of males who undergo DBS operations (Eusebio et al., 2013). However, the reason behind the difference in the frequency of individual ICBs across genders can arguably be

explained by psychosocial and cultural factors, which influence the type of impulsive behaviour and the openness to report it. For instance, the degree of dissatisfaction with sexual dysfunction in males is significantly higher than that of their female counterparts (Buhmann, Dogac, et al., 2017). Impulsive males may be drawn to engaging in problematic sexual activities as a result. This is not only because males report significant physical impairment in their sexual life after PD diagnosis, but also the impaired orgasm, which is less frequently reported in female patients. In addition, the higher age-related decline in libido among females (Hayes & Dennerstein, 2005; Lindau et al., 2007) may add to male dissatisfaction, leading to sexual isolation. This has been reported in male partners of female patients with PD (Lindau et al., 2007). Therefore, having a higher frequency of hypersexuality in male participants is influenced by factors other than their tendency to develop impulsive behaviours resulting from PD. Of note, it has been suggested to consider a higher cutoff point for hypersexuality in males among non-PD cohorts (Kalichman & Rompa, 2001). The same approach can benefit DBS-PD studies by reducing the effect of other factors in changes in hypersexuality. As for other ICBs like compulsive gambling, genetic studies (de Castro et al., 1999) and PD cohort studies have provided some insight into the matter (Voon et al., 2006, 2007). However, their findings either require replications or suffer from insufficient statistical power. In general, among their findings, novelty seeking and psychiatric comorbidity, which are more common in male patients (Evans et al., 2006; Gjedde et al., 2010; Lilleeng & Dietrichs, 2008), partly explain the difference. Consistently, patients who were prescribed psychotropic medication in the CRISP Study had a higher frequency of ICBs, except for hypersexuality and compulsive gambling, male-dominant ICBs in the CRISP study. Given the nonsignificant higher frequency of clinical cases of anxiety, depression and apathy in male participants, these findings highlight the role of psychiatric comorbidities and under-prescription of psychotropics in the frequency of individual ICBs.

5.3.6 Relationship of ICBs and Psychiatric Outcomes

This leads us to the following discussion subject: the difference in ICB frequency in clinical depression, anxiety and apathy subgroups. Binge eating, hobbyism-punding and DDS were more common in the clinical anxiety subgroup. However, among the remaining ICBs, only compulsive shopping showed a similar trend for anxiety. As for clinical depression, compulsive gambling showed only a trend, whereas others were significantly more common in the depression subgroup. Compulsive gambling, hypersexuality and DDS were significantly more frequent in the clinical apathy subgroup. However, in a regression analysis among all measured

psychiatric comorbidities, only depression and a higher score on the negative urgency trait significantly predicted the higher ICDs total at baseline. These findings about depression (Eisinger et al., 2022; Kim et al., 2013; Merola et al., 2017) and personality traits (Hernandez-Con et al., 2023; Pham et al., 2015) being a risk factor for developing impulsivity in PD patients are reported in other studies. Even the risk of dopaminergic medications to develop ICBs that are reported by others is thought to increase with depression (Marín-Lahoz et al., 2019). A secondary analysis of the PPMI study reported that depression and DA use were independently associated with the presence of ICDs, with the former preceding the ICDs (Marín-Lahoz et al., 2019). It is challenging to determine if depression symptoms are indeed reactive depression resulting from PD debilitating effects or if it results from PD underlying pathology. Depression is also thought to result from an impairment in the reward circuitries.

Depression and ICBs share mild to moderate cognitive impairments resulting from ventral striatal dopaminergic neurodegeneration, mesolimbic and mesocortical denervation and subsequent degeneration of serotonergic neurons in the raphe nucleus (Aarsland et al., 2012; Li et al., 2020; Vriend, Pattij, et al., 2014). Impulsivity in PD is linked with a reduction in cognitive and affective cortico-striatal networks (Carriere et al., 2015; Ruitenberg et al., 2018). PD patients with compulsive gambling have shown a reduction in grey matter in the orbitofrontal cortex (OFC) (Cerasa et al., 2014), a region which is involved with hedonic processing of reward and pleasure (Radcliffe Hospital et al., 2005). Among all regions, the OFC has direct connections to the amygdala, cingulate cortex, and dorsolateral prefrontal cortex (DLPFC) (Zhou et al., 2021). All are variably involved in decision-making, impulsive behaviours and emotions (Golchert et al., 2017; Tajima-Pozo et al., 2015; Zhou et al., 2021). Punding in PD patients has also been shown to be associated with a reduction in prefrontal cortical thickness (Markovic et al., 2017; Rajalingam & Fasano, 2023).

Furthermore, neurobiological perspectives will be briefly discussed to understand the relationship between these regions and the role of mood symptoms in impulsivity. The motivational opposition framework predicts the combination of negative affective symptoms and appetitive behaviours in ICBs (Boureau & Dayan, 2011). To illustrate, this framework states that dopamine and serotonin modify positive and negative affective events, respectively. The oppositional interaction of the two systems that modulate dopamine and serotonin is supported in animal studies. In these studies, serotonergic lesion lesions weakened the effects of dopamine agonists and antagonists on impulsivity, indicating the non-exclusive role of dopamine in ICBs (Cardinal et al., 2001; Winstanley et al., 2005). It has also been reported that

increasing serotonin manifested more avoidant behaviours (Di Rosa et al., 2022). These findings also explain the development of ICBs in new PD patients who have not started DRT, as discussed (Smith et al., 2016). The mood symptoms resulting from serotonergic neurodegeneration may explain ICBs in the first years following the onset. At a later stage, such as in the current cohort, serotonin deficit may become more critical in manifesting impulsive behaviours when the disease has progressed. Nevertheless, these findings indicate that in clinics, patients must be screened for depression as it enhances the risk of developing ICBs.

5.3.7 Predictive Factors of Impulsivity at Baseline

Negative urgency personality traits, depression, anhedonia and apathy were found to have potential predictive value for the presence of ICBs at baseline. As for personality traits, others have found associations between several traits and impulsivity (Castelli et al., 2006; Castelli, Perozzo, et al., 2001; Lewis et al., 2015; Lhommee et al., 2017; Mao et al., 2018; Pham et al., 2015). However, in the CRISP study, negative urgency was only predictive of positive cases of compulsive gambling at baseline. Others have reported strong associations between negative urgency traits and compulsive gambling in PD (Lim et al., 2008) and non-PD cohorts (Quintero et al., 2020; Willie et al., 2022). Other personality traits have been reported to be associated with compulsive gambling in PD, including novelty seeking (Lim et al., 2008) and sensation seeking (Balconi et al., 2018). In the same multivariate regression model, apathy (AES) and the ability to experience pleasure (anhedonia) were measured on the SHAPS and were predictive of positive cases of compulsive gambling at baseline. In addition, higher apathy scores also predicted positive cases of DDS. However, different psychopathological constructs of apathy are not captured by the AES which is used in the CRISP study. For example, authors of a metanalysis of 6 non-PD cohorts (N=3743, mean age [SD]=33.3 [10.4]) with impulsivity and apathy reported that social apathy on the Apathy Motivation Index (AMI) showed a significant negative correlation with the motor impulsivity on the Barratt Impulsivity Scale, which does not exist on the AES (Petitet et al., 2021). This finding suggests that if an individual ICB relies on motor impulsiveness (i.e., acting quickly), it may not correlate with apathy on the AES or when impulsivity is measured on other screening tools. According to Barratt's theory, impulsivity can be traced back to three primary substrates: motor, cognitive, and non-planning (Barratt ES et al., 1985). However, this approach to measuring impulsivity has been challenged by a complementary bi-dimensional approach, including cognitive and behavioural impulsivity, which has led to the introduction of the Impulsivity Scale -12 items (Kahn et al.,

2019). This bi-dimensional approach can be more suitable for PD cohorts, given their mobility problems, and more comparable to the instruments used in the CRISP study. Although it is not commonly used in the PD cohorts.

Furthermore, the results of the CRISP study are more in line with the circuit-specific hypothesis, which claims apathy and impulsivity to be two distinct syndromes, with the former resulting from dysfunction in the anterior cingulate circuit and the latter resulting from the orbitofrontal cortex (Mega & Cummings, 1994). Hence, given the connectivity of these two regions on the one hand and the extensive neurodegenerative nature of PD, the significant prediction of gambling and DDS by apathy helps to localise the pathology of compulsive gambling and DDS. It also emphasises the distinct psychopathology underlying individual ICBs.

Moreover, the high score on the SHAPS, indicating anhedonia, was also predictive of positive cases of compulsive gambling. Considering the common underlying pathology and overlapping symptoms between anhedonia and apathy, impairment in the ability to make effort-based decision-making can be the theme of their role in impulsivity. Apathy and anhedonia both manifest a lack of motivation, also known as amotivation, in psychiatric disorders like major depression disorder and schizophrenia (Bortolon et al., 2018) and neurologic disorders like PD and Alzheimer's disease (Erkkinen et al., 2018). Indeed, lack of motivation, as defined earlier in *Chapter 1*, is commonly referred to in neurological disorders as apathy, whereas in psychiatric disorders, using apathy or amotivation as a context for anhedonia and negative symptoms is common as well (Husain & Roiser, 2018; Petitet et al., 2021). Furthermore, anhedonia has been redefined over recent decades in psychiatric contexts to include "loss of interest in previously interesting activities" as a motivational construct (Treadway & Zald, 2011). The common dysfunctional brain networks in apathy and anhedonia have been extensively studied in animals and humans. These networks stretch in between several brain regions, including but not limited to basal ganglia, anterior cingulate cortex and orbitofrontal cortex (Kirschner et al., 2021; Knutson et al., 2015; Moretti & Signori, 2016). These studies have investigated data collected on behaviours (Foley et al., 2017; Isella et al., 2002; Martínez-Horta et al., 2014), neuroimaging (Radziunas et al., 2020; Saeed et al., 2020; Scharre et al., 2018; Wen et al., 2016), localised brain lesions (Blume et al.,2017; Costentin et al.,2019), and DBS (Castelli et al., 2007, 2007; Castelli, Lanotte, et al., 2007; Foley et al., 2017; Okun et al., 2014) to understand the dysfunction in reward processing and its implication in decision-making that lead to mental and physical effort. Of note, as it is challenging to measure

pleasure in animals, their motivations to engage in pleasurable activities reflect experiencing pleasure, and the opposite is considered in human subjects. However, pleasure and motivation cannot be considered the same in real-world clinical practice where cultural, capacity, comorbidity, financial, and legal matters play various roles. In addition, these two syndromes also share the same networks with impulsivity and cognitive impairment, executive dysfunction specifically (Balconi et al., 2018; Barratt ES et al., 1985; Petitet et al., 2021; Willie et al., 2022). Therefore, a cognitive impairment comorbidity can explain the lack of ability to experience pleasure and motivation when apathy and anhedonia show predictive values for impulsive behaviours. Indeed, in the CRISP study, apathy scores showed a significant moderate positive correlation with cognitive items on the PDQ-39 and UPDRS, I. The correlation between the cognitive-related items and anhedonia was also significant and positive.

Depression which predicted hypersexuality, compulsive shopping and hobbyism-punding at baseline has been reported to impose a higher risk under influence of DAs in non-DBS cohorts (Marín-Lahoz et al., 2019). However, due to lack of correlation between DA use and ICBs in the current cohort in line with findings of others (Kim et al., 2013; Merola et al., 2017; Pallanti et al., 2010), depression and impulsivity are thought to share underlying mild cognitive impairment (Dobkin et al., 2011; Strutt et al., 2012a). The cognition impairment that leads to impulsivity may impact reward processing and option generation. Option generation refers to the cognitive ability to generate options for given scenarios. As an illustration, patients are questioned about their plans for a sunny day. The conflicting association between apathy (lack of motivation) and impulsivity, or in other words, a hypodopaminergic and a hyperdopaminergic state, respectively, warrants alternative explanations. It has been suggested that separable cognitive impairment/executive dysfunctions leading to distinct deficits in option generation, option selection, action initiation or inhibition and learning can simultaneously lead to both apathy and impulsivity (Demeter et al., 2017; Sinha et al., 2013; Zgaljardic et al., 2007). In a case-control study, the authors failed to find any difference in the ability of option generation between PD patients on DAs and healthy cohorts (n=35 vs n=29)(Ang et al., 2018). However, the authors reported that DA significantly increased the number of options generated in PD patients.

5.4 ICBs After STN-DBS

The subject of the following discussion is the change in impulsivity at 6-month follow-up (see *Table* 39-40). In line with several STN-DBS studies (Abbes et al., 2018.; Ardouin et al., 2006; Eusebio et al., 2013, 2013; Gee et al., 2015; Kim et al., 2013; Merola et al., 2017; Pham et al., 2015; Rossi et al., 2017a), the ICDs total, a sum of scores for 4 major ICDs on the QUIP-RS, significantly reduced 6 months after the operation. As for individual ICBs, the major changes found were the significant decline in hypersexuality and hobbyism-punding at the 6-month follow-up. Compulsive shopping and DDS showed a trend towards improvement. However, binge eating and compulsive gambling did not change 6 months after the operation. The significant difference across pre-defined groups at baseline reduced to a nonsignificant level, except for the ICDs total and hypersexuality in males, and hobbyism-punding in clinical depression subgroups remained significantly different. In addition, the improvement in the total ICDs total, hypersexuality and hobbyism-punding did not differ across PD onset and working status subgroups.

5.4.1 Improvement in Individual ICBs

The interpretation of results in the ICDs total on the QUIP-RS and QUIP, reported in other studies (Rossi et al., 2017; Santin et al., 2021; Wylie et al., 3611), is not ideal as individual ICBs respond differently to STN-DBS. This may be because of the involvement of distinct underlying cognitive and emotional domains (Barreno et al., 2019) and distinct responses to reduced LEDD, motor symptoms and STN stimulation (Scherrer et al., 2020). Alternatively, it may simply indicate less impulsivity in general and reduced cases of multiple ICDs. The number of multiple ICDs (>2 ICDs) cases was reduced from 7 (9.6%) at baseline to 2 cases (3.3%) at 6-month follow-up. The individual ICBs are discussed in more detail.

Current findings about positive responses of hypersexuality (Gee et al., 2015) and hobbyism-punding to the STN-DBS are in line with other reports (Lamy et al., 2022; Lhommee, Wojtecki, et al., 2015). Individual case reports claimed that initial activation of SNT-DBS in a female patient induced a tendency to hug and kiss clinicians, a behaviour which subsequently was replaced by prominent compulsive shopping and paranoic thoughts (Herzog, Reiff, et al., 2003). Importantly, STN is appreciated by recent studies to be a part of the glutaminergic posterior hypothalamic region through which it plays a role in various functional networks to control expressive behaviours under external and internal stimuli (Barbier & Risold, 2021).

Therefore, stimulation of STN in the associative or limbic region can affect abnormal activities in the limbic system, including septal nuclei (Benarroch, 2008). Indeed, hypersexuality has been reported to be mediated by septal nuclei in the limbic system (Gorman et al., 1992). Both electrical and chemical stimulation of the septal region can induce pleasure sensation and compulsive masturbation (Berridge & Kringelbach, 2015; Hariz et al., 2010). In the CRISP cohort, the immediate effects of implantation or activation of the device are not recorded. Ideally, considering the sophisticated functional anatomy of the STN, such conflicting findings about manic episodes or hypersexuality (Herzog, Reiff, et al., 2003; Raucher-Chene et al.,2008) must be investigated after gathering data on precise contact locations. This will be conducted in the CRISP study in due course.

Despite the role that the increased dopamine release plays in hypersexuality and other ICBs (Fang et al., 2015), the cognitive deficit is another aspect that must be considered when investigating ICBs' response to STN stimulation (Strutt et al., 2012a). Incorporating cognitive measures in such investigations is limited in the current study as neuropsychological results were not collected. However, the result of the cognition subdimension on the PDQ-39 is discussed later in this chapter.

Improvement in impulsivity after SNT-DBS is thought to be due to a reduction in total LEDD and DAs (Carriere et al., 2015; Halbig et al., 2009; Kasemsuk et al., 2017; Merola et al., 2017; Okai et al., 2011; Samuel et al., 2015) and improvement in prepulse inhibition (Gee et al., 2015). Prepulse inhibition occurs when weak stimuli prevent the dramatic response that follows more potent stimuli. This phenomenon is impaired in dysfunctional sensorimotor integration between cortical areas and basal ganglia in PD (Dubbioso et al., 2019) and other neuropsychiatric disorders such as Huntington's and schizophrenia (Geyer, 2006). A case-control study (N=21; PD n=11, healthy n=10) reported that STN-DBS resulted in the normalization of dysfunctional sensorimotor integration 6 months after the operation (Shukla et al., 2013). Several structures influenced by STN stimulation play essential roles in prepulse inhibition, including but not limited to the nucleus accumbens, hippocampus, amygdala and medial prefrontal cortex (Naysmith et al., 2021; Rohleder et al., 2016). The extent of disturbance in sensorimotor integration varies based on the degree of dopaminergic degeneration in basal ganglia and cortical cholinergic denervation on the one hand and cognitive impairment on the other (Magalhães et al., 2018). This heterogeneity can also explain the variation in ICB response to STN-DBS.

As for hobbyism-punding, current results in the CRISP study suggest that improvement in motor complications such as fluctuations and improvement in non-motor activities of daily living (ADL) on the one hand and a lower quality of life may simultaneously contribute to an improvement in hobbyism-punding 6 months after the operation. From a psychological perspective, the relationship between hobbyism-punding and quality of life may change depending on the demanding nature of activities. To illustrate, the lower self-scored quality of life on the EQ-VAS may contribute to the lesser engagement in physically demanding hobbyism and punding as a coping mechanism towards distressing disabilities (Garlovsky et al., 2016). This psychological premise is more in line with the findings of others who linked punding with attentional dysfunction and worse ADL scores (Hinkle et al., 2021). These results point to a limitation that low quality of life imposes on impulsivity, which is partly explained as a coping mechanism to the distress that resulted from motor symptoms and ADL.

Therefore, it is essential to grade the demanding nature of such activities to understand their relationship with quality of life and mobility status. Hobbyism-punding activities are not specified in the CRISP study; the QUIP-RS does not evaluate the physical nature of the problematic activities. Furthermore, the improvement in hobbyism-punding at the 6-month follow-up did not show any correlation with improved anxiety and negative urgency and worsened apathy. However, it showed a significant weak negative correlation with improving sensation-seeking traits. According to these results, hobbyism-punding improvement is associated with lesser improvement in sensation-seeking traits, which is not reported by others in the context of compulsive behaviours. The sensation-seeking and novelty-seeking traits are both reported to be associated with ICBs (Hernandez-Con et al., 2023; Pham et al., 2015); therefore, improvement in sensation-seeking should also coincide with the improvement in ICBs. This explanation comes from studies that linked the trait to dopamine-dependent ICBs.

Sensation-seeking has been linked to other addictive behaviours, such as alcoholism (Czerwinski et al., 1999) and gambling (Pettorruso et al., 2021) in non-PD cohorts. However, it is not clear if it has the same role in other ICBs, including hobbyism and punding in PD patients. Given that ICBs and sensation seeking are shown to result from a hyperdopaminergic state, the involved dopamine pathways and receptors under the effect of STN-DBS and Parkinson's medications in two conditions may differ. In addition, a mediating role of mild cognitive impairment should be considered. Although it has been reported that more purposeful behaviours like hobbyism were not found in patients with cognitive dysfunction (Hinkle et al., 2021), other hobbyism and punding are linked to frontal lobe dysfunction (Rajalingam &

Fasano, 2023). Whereas sensation seeking is shown to be reduced by ageing (Gjedde et al., 2010) and cognitive impairment (Norbury & Husain, 2015). In fact, sensation seeking was reported to reduce significantly in PD patients (n=106) when compared to a healthy control group (n=106) (Evans et al., 2006). This is not the case in other significant personality traits, such as negative urgency, which worsens with cognitive impairment, resulting in more ICBs (Um et al., 2019).

Furthermore, at baseline, sensation seeking showed a nonsignificant negative, weak correlation with all ICBs (except hypersexuality). This contrasts with reports that found sensation-seeking traits higher in PD patients with ICDs (Bayard et al., 2016; Pham et al., 2021). The conflicting results of the association between sensation seeking and ICBs in the CRISP cohort can be due to longer disease duration and DA optimisation. The effect of DAs is similar to impulsivity traits on the UPPS-P and the ICB score in patients with shorter PD duration (Drew et al., 2020). Therefore, clinicians change or reduce DA dosage over time, which is why there is a dissociation between impulsive behaviours and sensation-seeking traits. However, this is not the case for other traits. In current results, the improvement in the negative urgency showed a nonsignificant weak positive correlation with improvement in both hypersexuality and hobbyism-punding. The improvement in lack of perseverance also showed a trend towards a weak positive correlation with the improvement in the ICDs total in line with other studies (Brezovar et al., 2022; Pham et al., 2021). Other studies with longer follow-ups (average 4 years), which reported persistent punding, found an association between punding and obsessive–compulsive personality traits (Merola et al., 2017). To gain more insight into the relationship between personality traits and impulsivity in DBS candidates, it is necessary to include other personality traits according to these findings.

5.4.2 Little to No Change in ICBs

Furthermore, although others have found improvement 1 year after the operation (Gee et al., 2015), in line with current results of the CRISP study, binge eating is reported to be the least responding ICB to STN-DBS (Abbes et al., 2018; Kasemsuk et al., 2017). A case series study (N=14) reported that an increase in body mass index in PD patients 1 year after the STN-DBS was associated with dorsally located leads outside the STN (Eguchi et al., 2021). In the current cohort, binge eating scores were significantly higher in clinically depressed participants at baseline and showed a similar trend at 6-month follow-up. Of note, depression did not improve at 6-month follow-up. This result indicates depression to have a more common underlying psychopathology with binge eating and other unchanged ICBs than hypersexuality and

hobbyism-punding. In the perfectionism model of binge eating, one assumption links behaviours to low mood. According to this model, binge eating is a coping mechanism for depression (Sherry & Hall, 2009). Although it does not entirely fit binge eating in PD patients, the coping mechanism suggested by the model can provide a potential explanation for the lack of improvement in depression and binge eating in the current cohort. It is also suggested that anxiety sensitivity increases the frequency of problematic impulsive behaviours such as binge eating and substance abuse (DeMartini & Carey, 2011; Lejuez et al., 2006). This anxiety sensitivity is a cognitive tendency that exaggerates the interpretation of anxiety-related physiological arousal. Of note, it has been reported that this tendency is also significantly correlated with negative urgency traits (Guillot et al., 2014). Likely, anxiety sensitivity is not related to anxiety severity on the GAD-7. Others have reported anxiety to be strongly associated with binge eating in non-DBS PD patients (Rosenbaum & White, 2013). The anxiety scale, GAD-7, is reported to be a reliable tool in clinics. However, other scales, such as the Hamilton Anxiety scale, can be more useful to assess the relationship between somatic and cognitive symptoms of anxiety and impulsivity (HAMILTON, 1959; Johnson et al., 2019; Spitzer et al., 2006). This is due to the strong modulating effect of motor symptoms of PD on the relationship (Wen et al., 2016).

Another explanation for binge eating is the cognitive avoidance theory. According to this theory, binge eating is a habit that prevents negative emotions like anxiety from entering a person's consciousness (Pallister & Waller, 2008). However, the significant reduction in the GAD-7 scores in the absence of improvement in binge eating does not support the role of cognitive symptoms of anxiety. In addition, mood-related cortisol is reported to reduce 12 months after STN-DBS despite a significant increase in weight up to 6 months after the operation (Funct et al., 2012). Therefore, a direct effect of STN on the hypothalamus, with less hormonal change, can explain the ICB's response (Markaki et al., 2012). In problematic overeating in non-PD cohorts, nucleus accumbens DBS has shown promising signs of restoring inhibitory control (Shivacharan et al., 2022). The limbic region of STN contains glutaminergic neurons projecting into several structures, including the nucleus accumbens (Emmi et al., 2020; Prasad & Wallén-Mackenzie, 2024). How it responds to STN-DBS in the long term remains to be observed. Longer follow-ups of STN-DBS patients have produced more optimistic responses in individual cases (Abbes et al., 2018).

In contrast, others have reported that stimulation of the limbic region of STN reinforced the pursuit of high-calorie and sweet foods by activating food cue processing territory in the

salience network[27] (STN-DBS n=21 vs healthy control =19)(Steinhardt et al., 2022). Consistently, an increase in attentional impulsivity (on the BIS) was reported in participants (N=22) with leads located in the limbic region (medial) of the STN (Somma et al., 2022). Of note, it is not clear if cases with high scores for binge eating meet the criteria for eating disorders. Measuring weight, psychosocial and medical impact will also reveal the severity of binge eating. On the PICS, which incorporates the psychosocial impact, the frequency of patients with binge eating (above cutoff) non-significantly increased. This increase, despite stable depression and a significant reduction in anxiety scores, is worth clinical follow-up and further discussion. In the face of a significant improvement in other parts of UPDRS (except part 3) and quality of life, overeating may have been a positive expression of the participant towards the improvement. This would, of course, depend on the related personality traits like positive urgency and the effect of improvements on patients' experience of the world, also known as the field of affordance. Positive urgency was the only trait that significantly increased after 6 months. Furthermore, the field of affordance phenomenon has been observed in patients with obsessive-compulsive disorder following DBS (De Haan et al., 2015). According to the author, patients have more enjoyable choices in their environment because they feel less confined and limited by their symptoms.

Contrary to reports of a secondary analysis of a non-RCT and another prospective cohort (Kim et al., 2008), compulsive gambling was the least improved ICB in the CRISP cohort and other studies (Kim et al., 2013; Merola et al., 2017). However, the former study's data on pre-DBS ICBs was collected retrospectively, and the postoperative follow-up in both studies ranged from 1-6 years. Reports of a more extensive retrospective study (N=598) were in line with the current results of the CRISP study. The authors reported that compulsive gambling persisted following the operation and did not resolve until 2 years after the operation when an improvement was observed concomitant with LEDD total reduction (Ardouin et al., 2006). Regarding DDS, multiple studies, including case reports, have observed improvement in longer follow-ups (up to 2 years) (Ardouin et al., 2006; Eusebio et al., 2013; Witjas et al., 2005). In a case series study, others have reported mainly worsening in DDS (N=22)(Lim et al., 2009). In the latter study, participants' mean (SD) PD duration was longer than the two previous studies

[27] The salience network consists of brain regions that have the anterior cingulate and ventral anterior insular cortices as their cortical hubs. These regions activates simultaneously during various cognitive tasks (Seeley, 2019).

and the CRISP cohort, at 11 (5), ranging from 4 to 24 years. The longer PD duration can be attributed to the poorer response of DDS to DBS due to longer desensitisation duration. Prolonged habit and desensitisation are believed to make recovery more challenging, according to theories of desensitisation (Robinson & Berridge, 2003). An alternative explanation for the worsening of DDS is related to dopamine withdrawal plans. Reducing dopamine should only be done with the patient's complete agreement (Evans et al., 2004). In addition, some authors suggest that in cases of severe DDS and other addictive behaviours like gambling, the DRT reduction must take place immediately following the DBS activation as soon as a high-frequency stimulation is tolerated (Bandini et al., 2007; Funkiewiez et al., 2003). The reason for this is believed to be the psychotropic effects of high-frequency STN-DBS, which lead to decreased anxiety and fatigue and enhanced euphoria and motivation. However, the network-wide outcomes of DBS in vivo need to be investigated in neuroimaging studies incorporating precise contact location (Loh et al., 2022).

The persistence of ICBs following optimisation of DAs and improvement of personality traits after DBS can also be due to the lasting changes in the sensorimotor striatal network. It has been suggested that a weaker connectivity between the frontal lobe and basal ganglia on one hand and a heightened connectivity between the motor cortex and basal ganglia on the other leads to increased impulsivity (Ruitenberg et al., 2018). Of interest, the authors of a retrospective study (STN n=14 + GPi n=23) reported a significant difference in the results of a Stroop Task (Colour-word) in positive cases of ICBs after the operation (Kim et al., 2013a). Another retrospective reported the same difference in the Stroop task (colour-word) in their 10-year follow-up (Janssen et al., 2014). The Stroop task performance is correlated with the activation of the caudate nucleus and frontal cortex, including the dorsolateral prefrontal cortex (DLPFC) (Dunet et al., 2016).

Given that the last follow-up was completed 6 months following the operation, current results indicate that individual ICBs' responses to DBS differ at 6 months. Longer-term follow-ups have conflicting results, including unstable improvements in ICBs over time (beyond 1 year postoperatively) (Abbes et al., 2018), worsening of ICBs in a small cohort (N=22) (Şimşek Erdem et al., 2023) and relapse of resolved ICBs (Smeding et al., 2007). The heterogeneous period of follow-ups among participants (Abbes et al., 2018), variability in assessment tools including MIDI, Ardouin Scale, clinical notes and QUIP (Abbes et al., 2018; Şimşek Erdem et al., 2023; Smeding et al., 2006) and small cohorts interpret such conflicts as more challenging. In studies with long-term follow-ups (10 years and more), many patients are diagnosed with

dementia and are no longer comparable to new candidates for STN-DBS (Bang Henriksen et al., 2016; Healy et al., 2022; Janssen et al., 2014; Skapinakis et al., 2010).

5.4.3 Correlation of Characteristics of Participants and Psychiatric Symptoms with Changes in ICBs

In this section the correlation between impulsivity status and other variables is discussed with more focus (see *Table 41*). According to 6-month follow-up results, the improvement in ICBs did not correlate with age at operation, which aligns with the findings of others (Merola et al., 2017; Rossi et al., 2017; Santin et al., 2021). However, PD duration showed a nonsignificant weak negative correlation with improvement in all improved ICBs. Others in longer follow-ups have found younger age to be associated with more improvement in ICBs (Abbes et al., 2018; Kim et al., 2013; Merola et al., 2012). The reduction in total LEDD also showed a negative correlation with all improved ICBs but did not reach a significant level. The negative correlation with ICB improvement is reported by others (Janssen et al., 2014; Kim et al., 2013; Lhommée et al., 2018; Lule et al., 2012; Rossi et al., 2017). The correlation's non-significance level in the current cohort can be due to the follow-up time and the cohort size. Clinicians may not achieve the maximum reduction of medication and improvement of impulsive behaviours before 6-month follow-up.

On the other hand, a reduction in anxiety at 6-month follow-up showed a significant moderate positive correlation with the total ICDs and hypersexuality improvement. Other studies reported that anxiety improvement was also associated with improvement in ICBs (Kim et al., 2013; Pallanti et al., 2010; Somma et al., 2022). After reviewing 22 individual case reports, it was observed that anxiety worsened in participants with worsened ICBs (Demetriades et al., 2011). Furthermore, apathy, which was significantly worsened at 6-month follow-up, showed a significant moderate and weak positive correlation with the improvement observed in the ICDs total and hypersexuality. However, there was no correlation with the *de novo* cases of apathy (n=42). Both worsening of apathy and improvement of impulsivities are thought to be due to a reduction in LEDD and DAs (Bandini et al., 2007; Boon et al., 2021; Castrioto et al., 2022; Fisher et al., 2016; Kirsch-Darrow et al., 2011; Samura et al., 2020; Zoon et al., 2021). The likelihood of a common underlying DBS-induced cognitive impairment is reduced when ICBs are improved or stable 6 months after the operation. That is because worsening of ICBs is thought to be associated with mild to moderate cognitive impairment (Gronchi-Perrin & Vingerhoets, 2009; Rajalingam & Fasano, 2023; Siquier & Andrés, 2021). More on apathy worsening is presented in the following subsection.

5.4.4 De Novo Cases of ICBs

As for *de novo* cases, hypersexuality and compulsive shopping were the only ICBs with 0 cases (see *Table 42*). The 9 (14%) *de novo* cases of ICBs (ICDs + other related ICBs) included one case of compulsive gambling in females, three cases of binge eating (2 males), five cases of hobbyism-punding (3 males) and two cases of DDS (1 male). Others have reported individual cases of *de novo* hypersexuality (Romito et al., 2002), hobbyism-punding (Lamy et al., 2022; Santin et al., 2021), punding (Pallanti et al., 2010), compulsive gambling (Ardouin et al., 2006), binge eating and DDS (Santin et al., 2021). The initial explanation is merely the possibility that patients are not entirely open about their impulsive behaviour before the operation to avoid being disqualified for the DBS or ashamed of their behaviours (Houeto et al., 2002a). Furthermore, *de novo* cases of ICBs are thought to be due to changes in dopaminergic agents in the context of mesocorticolimbic denervation (Santin et al., 2021). The authors have discussed that DAs may be introduced or increased in some cases to control motor complications better. These patients with no history can develop ICBs. However, in the current cohort, DA use was reduced. Another proposed explanation is related to the effects of DBS. It is thought that in *de novo* cases of ICBs, STN-DBS increases sensitivity to DA-induced behavioural side effects (Smeding et al., 2007). In addition, the localisation of contacts is argued to influence the development of *de novo* cases of ICB or worsening. The area least associated with *de novo* ICBs is thought to be the sensorimotor region or posterior part of the associative region of STN (Dafsari et al., 2018; Eguchi et al., 2021; Floden et al., 2018; Liang et al., 2023; Ulla et al., 2011). This region is also reported to be the most common targeted area in STN-DBS therapy (Coenen et al., 2008). In addition, the immediate effect has been reported in the ventral part of the associative region of STN (Okun et al., 2009; Welter et al., 2014), and its long-term effect on impulsivity and mood symptoms is reported to be desirable (Petry-Schmelzer et al., 2019; Seritan et al., 2021).

Given the established association between impulsivity and mood symptoms, a baseline psychiatric profile must be considered to optimise contact localisation for a better long-term impulsivity-related outcome. In addition, patients with *de novo* ICBs were shown to have significantly higher scores on cognition, depression and anxiety, indicating a role of interaction of cognition and mood with the stimulation in the CRISP study. This interaction is reported by others; however, it is not well understood if the stimulation induces cognitive impairment or if it results from the natural course of progressive neurogenerative disease (Volkmann et al., 2010). The safety of STN-DBS for cognitive function has been reported in several studies

compared to alternative therapies (Castelli et al., 2006; Gruber et al., 2019; Heo et al., 2008; Smeding et al., 2011), with some reports of clinically insignificant deterioration in executive dysfunction (Aybek et al., 2007; Kim et al., 2014; Witt et al., 2008). The small number of patients with *de novo* cases did not allow a regression analysis. Such analyses can determine if patients with new post-DBS ICBs have different neuropsychological differences. As discussed, the role of cognition and psychiatric comorbidities are well-studied; however, further studies have to investigate their role in post-DBS new cases of ICBs using brain imaging techniques.

Furthermore, the *de novo* ICBs are associated with preoperative borderline, schizoid and schizotypal personality traits (Merola et al., 2017). Although no correlation was found between impulsive traits and *de novo* cases of ICBs, other studies emphasise the importance of measurable personality traits in understanding the effects of invasive brain interventions. The possible DBS effect can be inferred from the observed activation of emotion-related areas in the limbic system following STN-DBS (Ulla et al., 2011). This effect can modulate behaviours highly linked with the construct of personality. Lastly, the long-term follow-ups will provide more information if post-DBS *de novo* ICBs are persistent.

5.4.5 Predictive Factors for Post-DBS ICB Changes

In regression analysis, baseline anhedonia, measured on the SHAPS, showed statistically significant predictive values for improvement in total ICDs, hypersexuality and hobbyism-punding at 6-month follow-up. As discussed earlier, despite being considered a distinct morbidity, it shared several symptoms with apathy and depression. The predictive value of its high scores at baseline for improvement in ICBs, despite lack of improvement in depression and worsening of apathy, carries clinical indications. The underlying pathology of anhedonia in PD has to be briefly reviewed to understand the indication. Like apathy and depression, anhedonia in PD is thought to result from a disturbance in dopaminergic mesocortical and mesolimbic pathways, affecting the reward processing and motivational functions (Lemke et al., 2006). This is also manifested by loss of sociality and pleasure (Kaji & Hirata, 2011). Its prediction of positive outcomes indicates improvement in ICB cases in which reduced sensitivity to pleasure and loss of sociality are prominent underlying factors. Social life improves after improved motor symptoms following DBS (Lezcano et al., 2004; Lilleeng et al., 2015; Okun, 2012; Park et al., 2010), leading to improved ICBs. On the other hand, the disturbance in dopaminergic pathways may take more than 6 months to be modulated by the medication reduction and DBS stimulation.

Elation scores on the NPI-12 at baseline also significantly predicted improvement in hypersexuality. Upon replication and persistence at the end of the CRISP study, elation as a symptom of hypomania can be considered a predictive factor for improvement in hypersexuality. It can be directly due to the stimulation effect or reduction of Parkinson's medications. Others have reported the simultaneous development of hypomania and hypersexuality after the SNT-DBS (Romito et al., 2002). Others have failed to find such a coincidence in non-DBS PD cohorts (Morgante et al., 2016).

Clinically, it is difficult to distinguish hypersexuality in the context of an ICB from a manifestation of other psychiatric disorders, such as hypomania/mania, as proposed in the DSM-5 (American Psychiatric Association, 2013). The egosyntonic thoughts and behaviours in hypersexuality in the PD cohort separate it from obsessive-compulsive disorders (Bayard et al., 2016; Perrotta, 2023; World Health Organization, 2022). In addition, the frequently reported frontal lobe dysfunction in PD cohorts, which explains the lack of inhibition in hypersexuality, justifies classifying the behaviour as an ICB (Houvenaghel et al., 2015; Mega & Cummings, 1994; Moretti & Signori, 2016; Tichelaar et al., 2023, 2023). The neuroimaging findings have supported the notion of classifying hypersexuality under behaviour addictions, underpinning the dysregulation in dopaminergic and serotonergic systems (Yau et al., 2015). However, hypersexuality has been reported in L-dopa-induced hypomania (Goodwin, 1971; Maier et al., 2014; Nakum & Cavanna, 2016), and both conditions are thought to be induced by the medications (Maier et al., 2014; Oei et al., 2012). Therefore, hypersexuality as a manifestation of other conditions, such as hypomania/mania, cannot be ruled out.

In addition, in a simple linear regression analysis, sensation seeking showed a prediction trend of improving hobbyism-punding at the 6-month follow-up. The predictive potential of personality traits for post-DBS outcomes has been reported by others (Scherrer et al., 2020). However, the results of the CRISP study pointed to their predictive potential for improvement in impulsivity in general and cases of multiple ICDs. To illustrate, baseline cognition scores on the PDQ-39 and lack of urgency on the UPPS-P predicted multiple ICD cases. In simple linear regression, baseline negative urgency predicted a significant decline in multiple ICD cases. The improvement in the lack of urgency at the 6-month follow-up showed a trend towards a weak positive correlation with the improvement in the number of multiple ICD cases. The current findings at 6-month follow-up suggest that the role of depression is more significant in individual ICDs. However, personality traits seem to have a stronger association with the prevalence of multiple ICD cases.

5.5 Comparison Between the QUIP-RS and PICS Results

As shown in Table 25-29, 31 and 36-38, most analyses conducted in this thesis were also conducted for impulsivity results on the PICS. This section presents the major differences in the results of both scales at baseline and 6-month follow-up. Beginning with the baseline, the PICS showed a remarkably lower frequency of impulsivity for all participants when compared to the QUIP-RS. For example, the frequency of positive cases of the ICDs total (cutoff=10) screened by the QUIP-RS was 26% (n=19) *vs.* 12.3% (n=9) on the PICS. Additionally, 16.4% (n=12) and 4.1% (n=3) of the participants were positive for DDS and compulsive shopping on the QUIP-RS, respectively, but none on the PICS. The most prominent frequency differences for positive cases between the two scales were the frequency of hobbyism-punding, the ICDs total, and binge eating by 28%, 13.7% and 8.2%, respectively. When testing the difference in impulsivity across subgroups, as shown in *Table* 25-27 individual ICB frequency differed by the rating agency of the scale and psychiatric comorbidities. Based on current results, patients with anxiety and psychotropics will be more open to reporting hypersexuality-related activities in an interview.

In contrast, patients with clinical depression and not prescribed psychotropics will report their symptoms more openly on a self-rating questionnaire. For other ICBs, there was no clear indication. To illustrate, the frequency of positive cases of hypersexuality was slightly higher on the QUIP-RS than on the PICS for the total population. However, the difference in total scores of hypersexuality in the clinical anxiety subgroup was only significant on the PICS. In comparison, the difference in the total score of hypersexuality in the clinically depression subgroup was only significant on the QUIP-RS. This may indicate that patients with hypersexuality and clinical anxiety may need a semi-structured interview to be more open to sharing, rather than a self-rated questionnaire, such as the QUIP-RS. Especially when the anxiety was more strongly associated with the ADL and quality of life before and after the operation. Additionally, low quality of life and anxiety could have an impact on patients' completion of self-reported questionnaires (Cuijpers et al., 2010).

However, this was not the case for binge eating, for which the total scores were significantly different in the clinical depression and anxiety on the QUIP-RS. In contrast, the difference was only significant in the clinical anxiety subgroup on the PICS. This may also suggest that patients with binge eating and clinical depression may respond better to a self-rated

questionnaire than an interview, such as PICS. In fact, in the clinical depression subgroup, the difference in total score was not significant for any of the ICBs on the PICS, while it was statistically significant for all positive ICBs on QUIP-RS, except compulsive gambling. In addition, binge eating and compulsive shopping were the only two ICBs that were significantly different in the clinical anxiety subgroup on both scales, leaving hypersexuality as the only ICBs to be better candidates for semi-structured interviews.

As for apathy, like clinical depression, the total scores on the ICD total, compulsive gambling, hypersexuality and DDS were statistically significant on the QUIP-RS but not on the PICS. When comparing the total score of ICBs across psychotropic users, the difference was only positive on the PICS. The ICDs total on the QUIP-RS showed a significant correlation between age at operation and the pleasure scale (SHAPS) but not on the PICS. On the UPPS-P, the lack of perseverance showed a statistically significant moderate correlation with the ICDs total on the QUIP-RS but not on the PICS. However, the ICDs total on both scales were similarly correlated with the UPPS-P total score, negative urgency and positive urgency. Profiling participants to determine the best scale in terms of rating agents will help increase the efficiency of screening by reducing the tendency to conceal symptoms. However, such a comparison will require a more sophisticated study design and other screening tools. In selecting a screening tool, it is important to consider the role of psychiatric comorbidities and the type of ICBs according to the limited findings of the CRISP study.

For this purpose, scales incorporating various aspects may help profile PD patients. Other studies that used the Ardouin behavioural scale in PD (ABSPD) reported ICBs at lower frequencies like on the PICS in the CRISP study (Kim et al., 2013; Lhommée et al., 2018; Santin et al., 2021). The ABSPD includes 21 questions categorised into 4 parts: general psychological evaluation, apathy, non-motor fluctuations, and hyper-dopaminergic behaviour (Ardouin et al., 2009). The ABSPD is a comprehensive, standardised and valid scale for PD patients. The scale has a limitation in completion time (~ 2 hours).

Moreover, it is primarily intended for dopamine-dependent behaviours (Evans et al., 2019). Its interview-based screening may explain the difference in their results for individual ICBs. The frequencies of ICBs on the PICS, a semi-structured interview, are closer to what the three larger cohorts reported in the above studies. In addition, compulsive gambling was more common on the QUIP-RS, but the PICS showed similar patterns to those observed in a retrospective review of consecutive STN-DBS PD patients (N=598) at 1.1% (Ardouin et al., 2006). The authors reviewed the clinical notes in which the diagnosis was made during an interview based on the

DSM-IV. This may not be the case in other related ICBs, as the authors of a small cohort (N=24) reported that a 1-hour clinical interview revealed that 20% of patients had punding (Pallanti et al., 2010), which was relatively similar to the results on the self-rating QUIP-RS in the CRISP study. Also, DDS was reported at 16% in a consecutive case series (N=110), using the interview-based Minnesota Impulse Disorder Inventory (MIDI) (Eusebio et al., 2013). However, the severity ratings of impulsivity are not available on the MIDI (Evans et al., 2019). In addition, the motor and cognitive aspects in PD patients with impulsivity have been more often examined on disease-specific scales like the QUIP-RS (Martini et al., 2019; Siquier & Andrés, 2021) and the Ardouin scale (Martín-Bastida et al., 2021). This is important because mild cognitive impairment (Gronchi-Perrin & Vingerhoets, 2009; Siquier & Andrés, 2021), motor severity (Riley et al., 2018) and motor complications (Ricciardi et al., 2023) are considered significant covariates in impulsivity measures.

In contrast to compulsive gambling, results for both ICBs (Punding and DDS) were more consistent with the CRISP study results on the QUIP-RS than PICS. These results indicate that the frequency of individual ICBs may differ based on the assessment method and patients' level of insight or openness about the behaviour(s). It can be argued that ICBs with relatively more resisting difficulties, negative consequences and calming effects are less commonly reported in semi or full-structured interviews. This is at least before patients gain full insight into the problematic behaviour and become open to sharing it with the clinicians. When such properties are stronger in ICBs and associated with more symptoms of withdrawal syndrome upon resisting the temptation, such as DDS, patients may be inclined to a positive rating on a self-rated questionnaire in the screening process (Okai et al., 2013; Rabinak & Nirenberg, 2010). This is how patients are screened for ICBs on the PICS and QUIP-RS; however, the screening may start with an interview on other interview-based scales mentioned above. It should be noted that patients are guaranteed anonymity and privacy in all research settings. Therefore, in clinical practice, the result will merely rely on patients' openness about the problematic behaviour(s).

At 6-month follow-up, the difference across clinical anxiety and apathy subgroups was not analysed due to the small number of participants who scored above the corresponding cutoff point. However, in the clinical depression subgroups, the difference in the total scores on the ICDs total and hobbyism-punding remained significant on the QUIP-RS and non-significant on the PICS. However, the differences in total scores of all ICBs, especially ones that showed

a significant to nearly significant improvement were non-significant on both scales. The differences in the total scores across other subgroups were the same.

5.6 Outcomes of Other Psychiatric Symptoms at 6-Month Follow-Up

5.6.1 Anxiety

The frequency of patients with anxiety at baseline was lower than the frequency reported in other studies with smaller PD-DBS cohorts (N=40) at 16% vs 40% (Voon et al., 2005). It was also lower than the results of a systematic review of 49 studies of non-DBS PD cohorts, which reported a frequency of anxiety disorder at 31% (6%-55%). The reason for these differences may be the GAD-7. Contrary to ICB scales, clinicians administered anxiety scales (Stefanova et al., 2013) or ones based on DSM criteria (Pontone et al., 2011), generated higher frequency. Nevertheless, the heterogeneity in scales and cutoff points, on the one hand, and the heterogeneous nature of PD pathology, on the other hand, can also contribute to the disparities (Broen et al., 2016). The number of patients with clinical anxiety significantly reduced from 12 out of 73 recruited participants at baseline to 5 out of 61 participants who completed the 6-month follow-up. This improvement aligns with what the authors of a controlled cohort reported (Chang et al., 2012). However, the authors reported that early improvement in the state of anxiety was not stable beyond 1 year postoperatively.

Furthermore, anxiety at baseline and 6-month follow-up were positively correlated with quality of life, in line with finds of others (Boel, Odekerken, Geurtsen, et al., 2016; Voon et al., 2005; Witt et al., 2008). Anxiety at baseline was positively correlated with cognition, negative urgency, and anhedonia, all of which had the variably significant predictive potential for the presence of ICBs at baseline and their changes at the 6-month follow-up. PD-related anxiety is thought to be due to serotonergic and noradrenergic neurodegeneration preceding nigrostriatal dopaminergic loss (Gallagher & Schrag, 2012; Han et al., 2018; Thobois et al., 2017). It has also been suggested that anxiety can be secondary to psychosocial distress associated with motor and nonmotor symptoms of PD (Prediger et al., 2012). The CRISP study showed a significant improvement in anxiety, which suggests that preoperative anxiety may have been partly linked to fear of undergoing an invasive brain surgery. However, this cannot be shown using the GAD-7. Using scales such as the State-Trait Anxiety Inventory (STAI) (Chang et al., 2012) is recommended to distinguish recent anxiety from a chronic experience of anxiety

(Chang et al., 2012). In addition, the presence of other anxiety disorders, including panic disorders, was not investigated.

5.6.2 Depression

At baseline, the frequency of patients with clinical depression was 56% (40 out of 73), relatively close to what has been reported in a systematic review of the prevalence of depression in PD patients (40-50%) (Reijnders et al., 2008). The epidemiology of depression and other psychiatric symptoms in PD candidates for DBS therapy is not well reported, as the majority of studies only report changes over time without emphasising the frequency of mood symptoms and their corresponding management at baseline (Couto et al., 2014). In light of the progressive heterogenous course of PD and the higher prevalence of interacting comorbidities in older age, epidemiological studies of depression and other psychiatric symptoms can help understand their importance in DBS candidates. As a result, their management can improve as well. This is essential due to the strong association between depression with cognitive function and impulsivity, as discussed above and reported by others (Dobkin et al., 2011; Krishnan et al.,2019; Marín-Lahoz et al., 2019; Strutt et al., 2012; Vriend, Pattij, et al., 2014). The depression scores showed a trend towards a higher frequency in the working subgroup at baseline and a moderate positive correlation with cognitive function. It was also found to have a moderate positive correlation with quality of life measures. In addition, depression also showed a moderate correlation with negative urgency, another important factor with predictive potentials for baseline and 6-month post-DBS outcomes. The important role of depression management in controlling motor and non-motor symptoms (including suicidality) of PD has been demonstrated (Menza et al., 2009; Voon et al., 2008; Wang et al., 2009). Therefore, it is concerning to find that among 56% of patients with clinical depression, only 31% are on psychotropic treatments. That said, the information on receiving other modes of treatment, such as psychotherapy, group therapy, or exercise therapy, has not been collected. Lastly, depression scores on the PHQ-9 showed a significant correlation with depression-related items on other used scales, indicating their effectiveness in screening for depression in PD candidates for the DBS therapy.

At 6-month follow-up, there was no significant change in depression scores. However, the frequency of clinical depression declined (34%, 24 out of 61). Others have reported improvement in depression scores 6 months after the operation (Antosik-Wójcińska et al., 2017; Birchall et al., 2017; Chang et al., 2023; Chopra et al., 2014; Houeto et al., 2002; Straits-Troster et al., 2000). Possible reasons for this observation may be smaller cohorts (Houeto et

al., 2002; Straits-Troster et al., 2000), younger participants (Antosik-Wójcińska et al., 2017; Chang et al., 2023), and clinician-rated scales (Antosik-Wójcińska et al., 2017; Chang et al., 2023; Chopra et al., 2014; Houeto et al., 2002a). Unilateral STN-DBS also improved depression scores at 6 months (Birchall et al., 2017). No significant improvement were reported 3-12 months after the operation in a non-RCT (Active DBS n=121, subtherapeutic group =39) (Vitek, et al., 2020). The authors used Beck's depression inventory, a self-rated questionnaire. Using another self-rated questionnaire, a prospective and retrospective study (N= 63) reported no change in mood profile 1 year after their operation (Boel, Odekerken, Geurtsen, et al., 2016). According to other sources, periodic stimulation on and off does not affect depression (Castelli et al., 2006; Morrison et al., 2004). Severe depression and anxiety symptoms may not be experienced by those with higher education levels in the general population (Leigh et al., 2021) and PD patients (Chang et al., 2023). Other predictor factors have been discussed in *Chapter 2*. Similar to depression, the suicidality score did improve without reaching a statistically significant level.

Furthermore, worsening cognitive symptoms of depression have been reported 2-6 months after DBS operation in small cohorts (Chang et al., 2012; Houeto et al., 2002; Okun et al., 2014; Strutt et al., 2012). However, besides their small cohorts (up to 15 per each), considering the time it takes to activate the DBS device following the operation and to optimise its settings, it is difficult to draw firm conclusions from their outcomes. For the current cohort, it remains to be observed whether the 12 months post-DBS result will be promising. However, the current outcomes do not show worsening, except for 4 *de novo* cases (6.5%) at 6-month follow-up. Due to their small number, no further analysis can be conducted for *de novo* cases of clinical depression. It also remains to be seen if the location of lead contacts, total electrical energy delivered, and other DBS parameters correlate with depression scores at each time point. Nevertheless, depression is critical to be closely monitored postoperatively due to its strong association with cognitive function, motor outcome and quality of life.

5.6.3 Apathy and Anhedonia

The frequency of cases with clinical apathy and anhedonia at baseline was consistent with reports of others at 28% (n=21) and 34% (n=24), respectively (Antosik-Wójcińska et al., 2017a, 2017; Foley et al., 2017; Okun et al., 2014). Apathy is not shown to be different between DBS candidates and control PD cohorts (Kirsch-Darrow et al., 2011). However, apathy was more common in participants with lower total LEDD, a finding that has been reported by others (Lhommée et al., 2012; Santin et al., 2021). The total LEDD is reduced in PD patients to tackle

motor complications (Higuchi et al., 2015) and impulsivity (Samuel et al., 2015), which results in apathy. Since apathy was significantly more common in positive cases of ICBs, a hyperdopaminergic state, and more common in the lower LEDD subgroup, it emphasises the inverse relation between levodopa and apathy. The presence of apathy at baseline can also predict postoperative motor and non-motor outcomes (Denheyer et al., 2009; Maier et al., 2016).

Postoperatively, apathy scores significantly worsened, and the number of cases with clinical apathy dramatically increased from 21 out of 73 (28%) at baseline to 59 out of 61 (96%) 6 months post-DBS. This worsening trajectory following DBS has been previously reported by others, including secondary analysis of a randomised trial (n= 31) and a case-control study (n=48) 6 months following the operation (Foley et al., 2017; Kirsch-Darrow et al., 2011; Le Jeune et al., 2009; Okun et al., 2014; Witt et al., 2008). Abrupt reduction in the LEDD total has been proposed as the main reason for apathy worsening (Boon et al., 2021; Fisher et al., 2016; Zoon et al., 2021). However, the follow-up period for these studies is longer than 6 months. Others have reported that the trajectory of lead insertion is associated with worsening of neuropsychological outcomes including cognitive function in earlier follow-ups. Leads intersecting the caudate nuclei were associated with a higher chance of post-DBS cognitive decline (Witt et al., 2008). In the current study, apathy scores at the 6-month follow-up showed a significant moderate negative correlation with cognitive scores on PDQ-39, but the negative correlation with the total LEDD did not reach a significant level. The cognitive measurement used in the CRISP study is not highly specific, therefore, its clinical and research implications are limited. Variable associations between apathy and different cognitive domains have been reported based on the STN-DBS correlation. The authors of a neuroimaging study reported that 3 months after the operation, apathy increased in patients with semantic fluency impairment (Houvenaghel et al., 2015). A prospective cohort study reported improved executive function and stable apathy scores 3 months after the operation (Pham et al., 2015). In a consecutive case series (n=19), the authors reported that the significantly worsened verbal fluency was not correlated with the stable apathy scores 17 months postoperatively (Castelli et al., 2007). The authors suggested that the worsened verbal fluency was not related to prefrontal-basal ganglia network, as it is often reported to be disrupted in patients with apathy (R. Levy & Dubois, 2006; Moretti & Signori, 2016). Another explanation for the conflicting results could be the stimulation frequency, as lower frequencies have less impact on verbal fluency (Wojtecki et al., 2006). Apathy resulting from a cognitive dysfunction is termed cognitive apathy, and is

believed to result from a disruption in the link between the ventromedial prefrontal cortex, amygdala, and ventral striatum (Bick et al., 2017; Pagonabarraga et al., 2015). In addition, the position of contacts in the STN is associated with a worsening (Zoon et al., 2023). Contacts in the sensorimotor subregion to the limbic region have been reported to alter the prefrontal cortex in emotion induction tasks (Bick et al., 2017). However, the worsening of apathy is not correlated with a lack of emotion recognition but is thought to have other cognitive and behavioural substrates (Drapier et al., 2008).

Moreover, the less common apathy worsening following GPi-DBS compared to STN-DBS, as reported by several studies, indicates a potential direct role of STN stimulation in the worsening of apathy through its link to the prefrontal cortex (Lozachmeur et al., 2014; S. Zhang et al., 2022). The negative correlation between apathy scores and cognition, which also worsened in *de novo* cases of ICBs, emphasises the role of cognitive domains, including but not limited to inhibition processing speed and working memory (Evens et al., 2015; Jahanshahi et al., 2015; Merkl et al., 2017). It has been reported recently that jumping to conclusion bias resulting from impaired working memory in PD patients was associated with higher scores on the QUIP and poorer performance on the beads task (Pachi et al., 2023). The frontal dysexecutive syndrome is often associated with apathy in individuals with PD, which indicates that this symptom is attributed to the advanced stage of PD, which is characterised by extensive neurodegeneration (Volkmann et al., 2010). This improvement in impulsivity-related personality traits did not correlate with apathy. Findings of others have also ruled out a premorbid predictive value of personality traits for the trajectory of apathy in PD (McDonald, 2014; Pluck & Brown R, 2002). Lastly, other factors that are important in measuring the severity and are influential in apathy, such as social life, personality traits (Jao et al., 2016) and environment (Jao et al., 2016) are not included in the scale used in the CRISP Study, the AES. Notably, apathy showed a significant moderate positive correlation with lack of perseverance at baseline but a moderate negative correlation with the same trait postoperatively. This finding indicates that the association between apathy and the personality trait needs in-depth study to determine moderating factors such as function of different cognitive domains and DBS parameters.

Anhedonia, on the other hand, was significantly reduced at 6 months postoperative follow-up. Having certain common cognitive substrates with depression, apathy and impulsivity, these findings help in narrowing focus on potential cognitive domains and their associated brain region that may be modulated by STN stimulation 6 months postoperatively (Husain & Roiser, 2018; Kaji & Hirata, 2011; Watson et al., 2020). The mesolimbic pathway, linked to reward

and motivational processing, is thought to be modulated by STN stimulation (Lees et al., 2013; Thobois et al., 2010). However, optimising the precise positioning of the leads and the insertion trajectory can improve outcomes.

5.6.4 Quality of Life

In the current thesis, quality of life was analysed using the PDQ-39, which includes 8 subdimensions and a single value, the EQ-VAS. The single value EQ-VAS indicated a trend towards significant improvement postoperatively. Given its simple question about how one would rate the quality of one's life on that day and the lack of data on the underlying construct of health, it is best interpreted along other detailed scales (Feng et al., 2014). The scores of the summary index of PDQ-39 showed significant improvement, including a significant improvement in activities of daily living and stigma subdimension and a trend towards significant improvement in the mobility and pain experience subdimension. A retrospective study has also reported long-term post-DBS stability of quality of life (D. Floden et al., 2014). However, other subdimensions, including emotional well-being and cognition subdimension, did not show a significant change. This imbalanced improvement in motor symptoms *vs* mood symptoms may not be a pessimistic sign for the latter but an indication of their association with lasting complex neuropsychological conditions controlled by various cognitive-related brain regions. Improvement in quality of life measured on the PDQ-39 and other similar scales has been reported by others (Pusswald et al., 2019; Tykocki et al., 2013). The authors of another observational study (N=33) did not report improvement in stigma 12 months after the DBS operation (Jiang et al., 2019). Felt stigma plays a key role in the improvement of quality of life in PD, which must be taken into consideration in the management plan (Ma et al., 2016). In addition, psychoeducation has been proven beneficial in reducing mood symptoms perioperatively, partly because it reduces stigma and enhances sociability (Boel et al., 2016; Santos et al., 2017; Soleimani et al., 2014).

5.6.5 Implications of Outcomes of Personality Traits

Measuring personality traits is highly relevant when studying psychiatric symptoms, in particular, ICBs before and after the DBS operation. Several studies have reported associations between personality traits and anxiety (Castelli et al., 2006), depression (Kaasinen et al., 2001; Marín-Lahoz et al., 2019) and impulsivity (Brezovar et al., 2022; Lhommee et al., 2017) in PD patients. In the current study, personality traits including negative urgency and lack of perseverance significantly correlated with impulsivity and showed predictive potentials for the

presence of ICBs, as discussed. However, one of the interesting findings in the current study is related to utilising the UPPS-P in PD-DBS cohorts. As a self-rated and validated tool, the UPPS-P is an important questionnaire for all ICB-related studies in PD cohorts because all traits covered by the questionnaire have shown associations with problematic impulsive behaviours in PD patients (Bayard et al., 2016; Norbury & Husain, 2015). However, these cohorts were comprised of patients who were not candidates for DBS-PD, with shorter PD duration and controlled motor symptoms. All UPPS-P traits linked to impulsivity have been shown to be modulated by DA use (Riley et al., 2018; Sinha et al., 2013). Increased sensation seeking and lack of premeditation are reportedly associated with reduced D2 receptors in the midbrain. The D2 autoreceptors inhibit dopaminergic neurons; therefore, their reduction results in higher dopaminergic activity (DeYoung, 2013). In contrast, other traits like lack of perseverance and negative urgency are thought to result from lower dopamine activity (DeYoung, 2013; Meder et al., 2019).

According to current results, sensation seeking and lack of premeditation did not correlate with impulsivity, questioning their role in impulsivity among DBS candidates. However, this was not the case for negative urgency, lack of perseverance, or positive urgency, which were significantly correlated with impulsivity. The correlation between urgency and perseverance with ICBs in the DBS-PD cohort has been reported by others (Pham et al., 2015, 2021). In the current study, the use of DAs did not show any correlation with ICBs either. This could be due to an absence of association between optimised DA use and impulsivity in DBS candidates or more advanced PD pathology, as discussed. In addition, mild cognitive impairment might mask the role of certain personality traits in ICBs (Tichelaar et al., 2023). The three traits were also correlated with mood symptoms and carers' burden. When a new variable (UPP) was created from the three traits, outcomes correlated with impulsive scores on self-rated QUIP-RS and semi-structured interview PICS. However, this must be replicated when additional validated impulsive scales are administered to make a comparison.

Given that the full questionnaire has 59 items, removing items related to lack of premeditation and sensation seeking could help produce a shorter, more convenient version for the DBS-PD patients. During the CRISP study, participants gave negative feedback about the length of the questionnaire. Although there is a shorter version, it has not yet been used in the DBS-PD cohort and contains the same five traits with fewer items (Cyders et al., 2014).

5.7 Outcomes of Carer Burden

At baseline, there were patients (n=3) who did not have carers and others whose carers did not join the study. Regardless, the total number of carers at baseline (N=58) and 6 months post-DBS (N=43) were considered large enough to study the short-term effect of the DBS on the carer's burden. As expected, a large number of carers at baseline scored above the cutoff point (97%, n=56), indicating the negative impact of PD on the psychosocial aspects of their life. This has been reported in studies focusing on the carer's burden in PD cohorts (Ardle et al., 2022; Carrilho et al., 2018; Greenwell et al., 2015; Juneja et al., 2020; Leroi et al., 2012; Modugno et al., 2020; Morley et al., 2012; Okai et al., 2013; M. Peters et al., 2011; Tanji et al., 2013). Unlike the CRISP study, others have included the carer's demographics in their analyses (Morley et al., 2012; M. Peters et al., 2011; Tanji et al., 2013). The missing information limits the investigation as it was not feasible to take the gender, relationship, carer health and employment status into account. The CRISP study only focused on the impact of the DBS on the carer burden due to limited resources available.

Despite this, comprehending the level of PD impact and predictive factors that can be modified has provided valuable insights into managing PD. Per the current findings in the CRISP study and the literature, the caregiver's psychosocial status is most influenced by patients' physical well-being and non-motor symptoms, including sleep and emotional well-being (Dekawaty et al., 2019; Gülke & Pötter-nerger, 2022; Juneja et al., 2020; Tanji et al., 2013). In addition, as was observed in the CRISP study, most carers in relevant studies were female carers (Greenwell et al., 2015). In the CRISP study, the carers of female participants were missing more frequently. The reason for this could be the eagerness of female carers to participate in studies and to be involved in the management plan. In the current study, female participants also reported more lack of social support. Therefore, carers-related studies provide information on carers and indicate that female patients may require more clinical attention to compensate for the lack of social support (Soleimani et al., 2014; Solimeo, 2008; Vlagsma et al., 2017). It also calls for encouraging more male carers to participate to understand the impact of the PD on their burden. Besides patients' condition, carers' demographic, social and medical profiles can predict the burden. Having a positive relationship (D'Amelio et al., 2009), social parameters such as the size of the social network (Miller et al., 1996) and family support (M. Peters et al., 2011), mental health and financial stability (Williamson et al., 2008) are protective factors for the impact of PD on carers' burden. Conflicting results have emerged from

investigating social and demographic factors as predictors of higher burden (Greenwell et al., 2015). Others suggested that caregivers' resilience to reduce the impact of perceived stress and social parameters can be targeted for intervention to improve caregivers' burden. (Ertl et al., 2019; Tyler et al., 2020).

According to current outcomes, improving patients' quality of life and well-being at 6 months post-DBS has nonsignificantly reduced the carer's burden. Of note, despite having a nonsignificant reduction in total scores on the ZBI, the number of carers who scored above the cutoff point significantly reduced from 97% (n=56) to 27% (n=11). The improved status of the severity of motor symptoms showed a trend towards a significant correlation with reduced burden. Reduction in medications, mobility symptoms, and motor complications showed a correlation with a trend toward a significant level. This aligns with the findings of others who have reported a significant correlation in longer follow-ups (Crespo-Burillo et al., 2018; Gülke & Pötter-nerger, 2022; Westerink et al., 2023).

As discussed in Chapter 2, during the first few weeks following the DBS operation, patients may develop various adverse behaviours as a result of the stimulation, including euphoria, impulsive behaviours, and aggression, which may impact family relationships. These adverse events are not tolerated by some carers (spouses or professional carers) who find themselves unprepared to confront their challenges (Perozzo et al., 2001). Therefore, informing patients and carers of such incidents and their transient nature prior to operation can prevent collapse in relationships and increase carers' understanding. At 6-month post-DBS follow-up, the DBS effectively reduces cases who have scored above the cutoff point. This coincides with a reduction in medications and increased patient quality of life. It remains to be observed if the carer's burden will further reduce in the face of changes in the participant's general well-being at the end of follow-ups.

Furthermore, the time from operation was also found to be correlated with a lower carer's burden (Oyama et al., 2014). Given that the optimisation of DBS parameters can take months (Oliveira et al., 2021), at the end of the 12-month post-DBS follow-up, there will be enough data to investigate the protective and predictive factors for the carer's burden. According to current literature on the effect of DBS on carers, younger age (Soulas et al., 2012), favourable mental health and quality of life scores (Perozzo et al., 2001) and favourable preoperative relationship quality scores (Mosley, Breakspear, et al., 2018) were also shown to be associated with lower carers' burden following the operation. On the other hand, a favourable patient

profile to predict a lower burden includes younger age, shorter disease duration, lower LEDD, and fewer psychiatric symptoms (Crespo-Burillo et al., 2018; Gülke & Pötter-nerger, 2022).

5.8 Translational Outcomes of the Single Site Audit

The review aimed to investigate the effectiveness of the pre-DBS screening process for the presence of psychiatric symptoms; the outcomes have already informed changes to improve the quality of the process at KCH. Firstly, the retrospective cohort showed a significantly higher mean of age, disease duration, and frequency of patients with late-onset PD (>50) compared to the matched population from the CRISP study. The reason is believed to be that patients are currently being offered DBS surgery earlier in their disease course, as discussed. In addition, the CRISP study identified a higher rate of clinical depression before and after the operation, as expected. Although the difference was only significant before the operation, it is indicative that a brief self-rated questionnaire will identify more patients with clinical depression. In addition, the CRISP study identified a higher frequency of positive cases of ICDs after the operation that was statistically nearly significant. These results indicate that brief self-rated questionnaires handed to patients while in the waiting area or posted to their address before pre-DBS assessment will reduce the number of underdiagnosed clinical cases. This is crucial given the importance of both ICDs and depression, as discussed. Furthermore, having validated scale results will make it easier to conduct future relevant studies.

As for psychosis, the frequency of positive cases of psychosis at baseline was significantly higher in the retrospective cohort. This is probably due to having a longer PD duration, as psychotic symptoms are reported to appear more frequently in later stages (Chou et al., 2005; Gallagher & Schrag, 2012). It is believed to be for the same reason that the CRISP cohort showed a significantly higher frequency of subjects with reduced PD medications after the operation. Others have reported that young age and shorter PD duration are associated with a reduction in PD medications (Funkiewiez et al., 2003; Ghika et al., 1998). These results support the early consideration of DBS operation in cases with resistant motor symptoms and disturbing motor complications.

However, the reason for the lower frequency of psychiatric symptoms cannot be only due to a lack of valid screening tools, as some patients may be reluctant to reveal their symptoms in a clinic (Kennis et al., 2023; Porat et al., 2009). This can simply be due to the stigma attached to

psychiatric symptoms (Ma et al., 2016) or to avoid being disqualified for the treatment (Lilleeng & Dietrichs, 2008). Indeed, a potential reason behind having a higher frequency of psychiatric symptoms before operation in the CRISP study is that participants were assured of being eligible for the operation, with an already confirmed date for the operation. The review results indicate that the same should be replicated in regular practice. To illustrate, the pre-DBS assessment can be carried out to evaluate patients for severe psychiatric symptoms that disqualify patients from DBS. Then, to properly screen for clinical psychiatric symptoms among qualified patients, a set of brief self-rated questionnaires can be handed to patients to complete. The current outcome in the review indicated that the mean assessment duration before and after operation in the retrospective cohorts was significantly longer. The current workload in clinics impacts the pre-DBS assessment and follow-ups. Therefore, when proper assurance is given by the clinicians, a self-rated questionnaire can identify psychiatric symptoms without increasing the workload in clinics. The result of these self-rated questionnaires will produce raw data for relevant studies, and can inform optimal insertion trajectory and lead positioning. Repeating these questionnaires in post-DBS follow-ups can also inform studies of optimisation of the stimulation parameters.

The rating scales that should be added to the routine pre-DBS neuropsychiatric assessment include GAD-7 (anxiety), PHQ-9 (Depression), QUIP-RS (impulsivity), AES (Apathy) and SHAPS (Anhedoni). Completing all questionnaires will take approximately 15 minutes at a convenient pace for PD patients. The latter questionnaires, which screen for apathy and anhedonia, were added due to the high frequency of clinical cases at baseline and 6 months following the operation. They were not included in the retrospective review because they were not mentioned in any of the reviewed clinical notes, indicating a potential underreporting in the screening process.

5.9 Limitations

5.9.1 Limitations of the CRISP Study Based on Preliminary Outcomes

1. Neuropsychological profiles of patients were not collected. However, it would be feasible to conduct a retrospective review and analyse them.
2. The data collection process did not include a history of major comorbidities, past psychiatric history, or education level.

3. The routine preoperative off/on medication UPDRS, III is dated back one year in some cases. Given the disease's progressive nature, the cognitive and motor assessment may significantly change during this time period.
4. There is no control group. This could consist of PD patients on the DBS waiting list or cases who have refused DBS therapy. A control group could also consist of age- and PD duration-matched PD patients whose motor symptoms have responded to DRT.
5. The order in which the phone interviews were conducted might have impacted the rapport the research fellow needed to build with the participants. To illustrate, in the original order, patients were first interviewed for ICBs on the PICS. If the researcher had started with other scales such as UPDRS, GAD-7, or NPI-12 before finishing with PICS, it could have allowed him to establish a better rapport that would help participants be more open about the more sensitive questions on the impulsivity scale.
6. The interviews were conducted by a research fellow who was not in the participants' clinical team, which might have influenced the quality of the established rapport.
7. In the carers' case, only the burden was measured in addition to quality of life (EQ-5D-5L). To understand the impact of STN-DBS on carers' burden, it would be preferable to collect carers' demographics, relationships with patients, and comorbidities.

5.9.2 Limitation of the Thesis

1. This thesis did not include analysis of the DBS parameters essential for understanding their effects and predictive potentials for post-DBS outcomes.
2. The UPDRS, III results were not included, which is critical in understanding the association between primary outcomes and motor symptoms.
3. The underpowered cohort size at baseline and 6-month follow-up might have failed to find differences in some variables/outcomes.
4. The 6-month postoperative period may not have been long enough to achieve the maximum reduction in Parkinsonian medication, optimisation of DBS parameters, and the stimulations' modulating effect on networks involved with primary outcomes.

5.10 Future Direction in Investigating Clinical Response of Psychiatric Symptoms to STN-DBS In Observational Studies

By utilising current data collected for the CRISP study and a single-site retrospective review, this thesis provides vital information to answer lingering questions about the effect of STN-DBS therapy on impulsivity, psychiatric symptoms and carer burden. However, it also identifies the direction of future observational multicentre studies to enhance designs, tools, and data quality. Starting with the latter, understanding the effect of STN-DBS on outcomes of interest requires a comprehensive psychiatric history, personality traits, neuropsychological function, DBS parameters, and lead locations. It also must be highlighted that narrowing the focus on individual symptoms will reduce the burden on participants and carers and allow for a multi-faceted study of a given symptom. For example, although ICBs are mostly studied together, a tool for general impulsivity and another valid, specific tool for a given ICB would allow for a more detailed investigation that fits a time- and resource-efficient research project.

Furthermore, the instruments used for screening, diagnosing, or rating severity would provide more precise and valid outcomes if specifically designed for a given symptom. Such tools cover many domains and perspectives that others do not cover. For example, the Ardouin scale provides comprehensive information on impulsive behaviours that other available scales do not.

Finally, the design of studies could be improved by the addition a control group. In DBS-PD cases, a control group might impose many difficulties for several reasons. For example, the non-DBS PD group may have less severe PD. However, patients on DBS waiting lists in multicentre studies could be suitable candidates in the control group. In addition, patients who refuse DBS for personal reasons could also be candidates for such observational study.

Establishing a shared database by all UK DBS centres was a signficant achievement during my PhD project that can add quality to future relevant research. Collaborating between DBS centres to recruit larger cohorts and use unified scales and questionnaires will be made easier with this database.

5.11 Pandemic Halt and Recommendations for Possible Future Pandemics.

The COVID-19 pandemic and the related lockdown were announced in March 2020. This coincides with the early stages of setting up the CRISP study, a multicentre project involving DBS operations in seven clinical centres, mainly serving people above 50. Even though the research team did their best to conduct online meetings and managed to complete a draft protocol, the study was suspended due to uncertainty surrounding resuming surgical procedures. The pandemic, therefore, significantly affected our study at both individual and organisational levels. Below is a summary of how the lockdown impacted the CRISP Study.

All DBS surgical implantations were entirely stopped in March 2020. This meant we could not determine a start date for our IRAS application form. Additionally, the Cambridge DBS centre left the study due to changes in circumstances.

In addition, there was a significant delay in responses from copyright holders of scales and questionnaires (individuals and organisations), which was justifiable given the circumstances. As a result, some scales had to be replaced with ones in the public domain. More information on the chosen scales is presented in Chapter 4. During the lockdown, with the help of my research team, supervisors and the chief investigator, I managed to take forward the process of ethics and research and development department (R&D) sponsorship applications. However, departments' lack of staff and COVID-related issues immensely slowed the process. The last day of the lockdown was in December 2021. The study was granted ethical approval to secure approval of the capacity and capability (C&C) from all individual participating centres before recruiting. This meant the study could begin recruiting at centres that had finished C&C checks. Two centres completed it within a few days, but unfortunately, others took weeks to months to complete the C&C. It was explained that the delay was due to a shortage of staff and a backlog. As a result, numerous COVID-19-related studies were prioritised more than the CRISP study. The backlog did not just impact the CRISP study by delaying the necessary approvals but also by delays in recommencing operations. DBS-STN in PD did not rank high on the priority list for theatre and surgical time compared to other cases. In addition, the mandatory quarantine period before operation, social distancing, and COVID-19-related cases reduced the number of available beds in each centre. Significantly, even after recruitment began at each centre, the number of scheduled DBS surgeries was lower than before the pandemic.

The pandemic significantly impacted the study's course in many other ways once it had started. To demonstrate, patients were given short notice about the next available surgery slot. As a result, the recruitment window was very limited for many patients. An amendment was therefore needed to change the recruitment time from "before the operation" to "after the operation, before DBS activation". For the same reasons, the number of patients undergoing surgery was very small; therefore, the recruitment end date had to be extended twice. The protocol underwent other changes and amendments unrelated to the pandemic. A minor amendment enabled patients to receive questionnaires via email rather than mail. Despite these significant obstacles, the CRISP study is still recruiting. However, I was not able to use all the data that will be collected as I approached my submission deadline. Furthermore, no articles have yet been submitted for publication due to the recruitment start-up delay and slow process. However, the preliminary results were presented at the UK DBS meeting, DBS conference in Grenoble, France, and Royal College Psychiatrists Conference in London.

In a protocol template that all researchers receive from their Research & Development office, there is a thoughtful outline of all sections that a researcher must consider and complete before returning the protocol for an R&D sponsorship application. It is evident that individual historic events, such as the development of the Nuremberg Code, have shaped current versions of protocol templates over time across the globe (Spellecy & Busse, 2021). Whether to improve scientific quality or avoid legal, financial and ethic-related issues, protocols, templates, and policies constantly evolve (Altman & Simera, 2016). Therefore, it should be necessary to consider a potential global crisis such as the COVID-19 pandemic when updating research-related protocols and policies. To this end, I present several points for consideration based on my experience during the pandemic.

- Researchers should benefit from courses and workshops on managing unforeseeable issues as part of their doctoral-taught educational courses. For instance, these workshops should inform students about the resources and alternatives available for various stages of submitting for ethics approval and other study-related permits.
- For academic projects where students have limited time, copywriting owners should provide an express pathway to request permission. Such pathways would not be affected by pandemics as all information is categorically entered into an online form, and decisions are automatically made.
- Study protocols should be written as pandemic-friendly as possible. This hugely depends on the nature of individual projects. Therefore, a section for unwanted crises,

like a pandemic, should be inserted in all protocol templates. This is especially necessary for studies that extend over a long period.

- When selecting assessment tools, various forms of each tool must be acquired. To illustrate, for the NPI-12, there should be an informant rating, self-rating and an electrical version. This is in case participants cannot attend the clinic due to a lockdown. To make this feasible, research institutions must provide researchers with an online platform to utilise it.
- In processing funds or applying for grants, consideration should be made for a sudden halt for exceptional reasons, such as a pandemic, with a plan to reduce financial consequences for projects and research members. The cost of a pandemic immune fund could be reduced by designing pandemic-friendly protocols.
- For students staying in the UK on tier 4 student visas, such a sudden halt that lasts for months can be catastrophic psychosocially and financially. Having a contingency arrangement for natural disasters between sponsoring universities and the Home Office, which becomes effective in certain circumstances, would assist students in overcoming the burden of uncertainty and frustrations. I, fortunately, had no such issue, as there was adequate time left before my visa expiration date. However, this would have become an issue if the pandemic had started later in my study period. This has undoubtedly impacted many overseas PhD students.

Chapter 6: Conclusion

In the following sections, a brief conclusion for outcomes related to characteristics of patients, ICBs, other psychiatric symptoms and quality of life, the burden of carers before and after the STN-DBS.

Regarding age and PD duration, the current cohort shows that DBS is being considered earlier in the course of PD in participating centres. In addition, the literature does not support considering advanced PD as a disqualifying factor for DBS in the absence of moderate to severe cognitive impairment and severe psychiatric disorder. The proportionally appropriate inclusion of both genders and ethnic minorities remains to be studied.

In ethnic minorities, the potential reasons behind lower research participation must be studied to find a solution. In the meantime, relevant studies with different objectives can contribute by describing details that will inform research, such as the ethnicity and gender of participants who refused to enter their studies. In addition, general practitioners and local clinical teams must be guided to encourage consideration of the procedure to address the lower referral rate in females and ethnic minorities.

As for the safety of the DBS procedure, it is thought to be safe due to the low rate of serious adverse events post-DBS. However, the CRISP study could not properly inform the immediate post-DBS adverse events as the data was not gathered.

When compared to other PD-DBS cohort studies, the frequency of ICBs was remarkably higher in the CRISP Study. The frequency of ICBs in the semi-structured PICS was more consistent with the results of studies with large cohorts and interview-driven data. However, binge eating and hobbyism-punding remained high even in PD-DBS cohorts.

Furthermore, it has been shown that as the age and duration of PD increase, so does the frequency of ICBs. Moreover, the lack of association between PD medications and impulsivity, which is observed in the CRISP Study, is not universal for all ICBs, as DDS has been linked to the severity of motor symptoms and higher total LEDD. In addition, studies of premorbid vulnerabilities in a subset of PD patients reveal more about the relationship of dopamine activity with impulsivity in the early stages of the disease. Nevertheless, the association of ICBs (except DDS) with late-onset PD, above LEDD median indicated a potential role of advanced neurodegenerative disease and involvement of cognitive domains.

Studying the relationship between work and social functioning provided insight into the severity of impulsivity and potential protective factors.

Significantly, gender influences the manifestation of impulsivity. Others have suggested that seeking help in patients is the reason behind the higher frequency of individual ICBs in one gender. Furthermore, depression showed predictive potential for baseline high scores of hypersexuality, compulsive shopping, and hobbyism-punding. Emotional and cognitive impairments can modulate the association between depression symptoms and impulsivity. Cognitive impairments are also linked to the predictive potential of apathy and anhedonia for the presence of DDS and gambling. However, a more specific cognitive assessment is required to investigate cognitive function's role in impulsivity.

Moreover, among personality traits, the negative urgency trait was predictive of compulsive gambling as well. It is also noteworthy that different constructs of comorbidities might have distinct influences on their relationship with impulsivity, which might be overlooked if the scale does not cover them. Therefore, studying cognitive function using validated scales and neuroimaging studies is required to understand the relationship between psychiatric symptoms and problematic impulsive behaviours.

At the 6-month follow-up, individual ICBs respond differently to STN-DBS. As reported by others, hypersexuality and hobbyism-punding reduced the most, and binge eating and compulsive gambling changed the least. A reduction in impulsivity, in general, is a noticeable outcome at 6-month follow-up, resulting in fewer multiple ICD cases. Among measured psychiatric symptoms, improvement in anxiety at 6-month follow-up correlated with improvement in hypersexuality and hobbyism-punding.

On the other hand, quality of life improvement may arguably impose risk for less improvement in individual ICBs. As for ICBs that had little to no change, it is suggested that depression and apathy have a role that various cognitive and psychological models can explain.

Improvement in ICBs shows a trend towards an association with shorter PD duration and higher reduction in total LEDD, but not with younger age. Furthermore, worsened apathy was associated with improvement in impulsivity, as reported by others. The 6-month follow-up is crucial in examining short-term post-DBS clinical response; however, the 12-month follow-up will reveal lasting clinical outcomes.

Anhedonia and elation showed the most significant predictive value for positive ICB outcomes among measured psychiatric symptoms at baseline. Anhedonia may distinguish patients whose impaired social life and pleasure-experiencing abilities significantly impact their well-being. Therefore, when DBS improves those aspects by reducing motor symptoms, it may also reduce certain ICBs in a psychosocial context. Elation, on the other hand, indicates that hypersexuality due to impulsivity needs to be distinguished from a manic symptom. As for *de novo* cases of ICBs, 10 new cases of ICBs were observed. However, the small number did not allow further analysis. Furthermore, outcomes indicated a potential role of cognitive deterioration in the development of ICBs.

In the CRISP study, the lower frequency of clinical anxiety at baseline can be related to the self-rated questionnaire and heterogeneity in PD pathology and cohorts. Patients with anxiety may report symptoms more often in interviews than on self-rated questionnaires, in line with the conclusion that was made when comparing the two ICBs scales. In addition, a scale that distinguishes recent and prolonged anxiety experiences can determine if the anxiety is related to fear of the invasive operation. Nevertheless, the significant improvement in anxiety shows that the anxiety at baseline might have been related to the fear of the surgery and low quality of life related to poor control of motor symptoms and medication-induced complications. Furthermore, the frequency of anhedonia, which has overlapping symptoms with depression and apathy, was consistent with the other studies. However, its scores significantly reduced at the 6-month follow-up, unlike apathy and depression. Depression, on the other hand, showed a high frequency at baseline. Depression not only impacts the daily living of patients and carers, but it also has potential predictive value for post-DBS outcomes. However, the frequency of clinical depression was remarkably higher than the frequency of patients on antidepressant medications. In addition, depression is considered a debilitating symptom due to being higher among working participants and being strongly correlated with cognitive function and quality of life. These findings suggest that it is essential to screen for depression and address it appropriately.

Furthermore, depression was also less responsive to DBS and its effects on motor and non-motor symptoms at 6-month follow-up. However, the number of participants with clinical depression and suicidality declined. Similar to depression and anhedonia, the frequency of apathy was in line with the findings of other studies. Apathy, however, worsened at 6-month follow-up. The worsening of apathy can be related to adverse cognitive effects of the procedure, the location of contacts, and the significant decline in the total LEDD following

the DBS. That said, the general improvement in impulsivity can rule out the DBS effect on cognitive domains shared in both apathy and impulsivity at 6-month follow-up in the CRISP study. However, the unchanged cognitive scores significantly correlated with apathy scores in *de novo* cases of apathy.

The cutoff selected to determine the score for the high burden of carers on the ZBI varies between studies. Despite choosing a moderate cutoff based on the literature, the frequency of carers with a high burden was very high at baseline in the CRISP study. It is not a new finding that carers of PD patients have a high burden. Nor was the trend observed between patients' quality of life and carers' burden. However, the significant post-DBS improvement in total scores and frequency of patients who score above the cutoff point at 6-month follow-up was beyond expectation. In addition, the more common female carer participation indicates that the current literature provides more information on female carers than their male counterparts.

Finally, to improve quality of pre-DBS neuropsychiatric screening scales, the practical addition of a number of brief and validated scales were evident to be essential.

6.1.1 Summary Points: The Narrative review

1- There is a large diversity in measuring tools with very different psychometric and normative properties for the same body of symptoms.
2- There are also a lot of terminology differences across many studies.
3- There is need for more a meta-analysis with narrow focus on individual psychiatric symptoms.
4- STN is the most common DBS Target at 94%.
5- Early Psychiatric outcomes are in favour of medical treatment, but not the long-term follow-ups
6- Psychotic symptoms are not uncommon after DBS (5-25%).
7- Mood alterations and apathy symptoms are common after DBS (10-45%).
8- Age, cognitive function and history are patient related risk factors.
9- Psychotic symptoms tend to return to baseline.
10- In longer term, depression symptoms mainly range from stable to improvement.
11- Beyond 5 years after surgery, mood remains mostly stable.
12- The prevalence of *De novo* cases are not uncommon at 8-15%.

13- Individual ICBs can have distinct predictive factors.
14- There are conflicting results about relation between DA use and impulsivity post-DBS.
15- DBS setting optimization to reduce psychiatric symptoms are possible if motor symptoms are not exacerbated.
16- Immediate post-DBS psychiatric AEs have potential predictive value for outcomes related to quality of life.

6.1.2 Summary Points: The multicentre Observational Study (CRISP Study)

1- The current cohort demonstrates that participating centres are considering DBS earlier in the course of PD. By doing this, the number of quality years can be increased before a late-stage cognitive impairment leads to ineligibility for the DBS operation.
2- The current cohort's male-to-female ratio and ethnic minority underrepresentation are concerns echoed in the literature. Tackling these issues requires work on several fronts, including individual-tailored consultations and institutional actions.
3- In the current cohort, the frequency of certain ICBs at baseline, such as compulsive gambling, hypersexuality and compulsive shopping, is similar to that of non-DBS PD cohorts. In contrast, binge eating and hobbyism-punding are more common. This was in line with reports of other PD-DBS cohorts
4- The heterogeneity of the disease and diversity in cohorts make it challenging to find a consistent relationship between age and PD duration with the frequency of ICBs.
5- Premorbid vulnerability to ICBs will have to be studied further to distinguish their role in certain ICBs from other factors.
6- Lack of antidepressant prescribing for depression in the current cohort is concerning, given its strong correlation with ICBs.
7- Due to either the sensitive nature of the ICBs or the lack of social impact of the ICBs, the PICS had a lower rate of positive cases.
8- The role of employment status as a protective factor requires further investigation.
9- The role of gender in manifesting certain ICBs requires in-depth investigation.
10- Depression with emotional and cognitive symptoms shows a predictive potential for baseline hypersexuality, compulsive shopping and hobbyism-punding.
11- Apathy and anhedonia showed predictive values for the presence of DDS and gambling. Their predictive potentials require further investigation with in-depth cognitive assessment.

12- The response of individual ICBs to STN-DBS varies at the 6-month follow-up.
13- Consistent with reports of others, the most significant changes were observed in hypersexuality and hobbyism-pounding, with binge eating and compulsive gambling remaining unchanged.
14- At 6-month follow-up, there was a correlation between improvement in anxiety and improvement in hypersexuality and hobbyism-punding.
15- Cognitive and psychological models explain the relationship of depression and apathy with ICBs demonstrating little to no change at 6-month follow-up.
16- Shorter PD duration and higher reduction in total LEDD, but not younger age, are associated with improvements in ICBs.
17- Patients with anhedonia could be identified as those whose impaired social life and pleasure-experiencing abilities have a significant impact on their wellbeing.
18- In a psychosocial context, certain ICBs may also be reduced when DBS improves certain aspects of daily life through motor symptom reduction.
19- It is essential to differentiate hypersexuality caused by impulsivity from that of manic symptoms, as indicated by the observed predictive values of elation.
20- More extensive investigation is required to understand the relationship between personality traits and ICBs.
21- Individual ICBs and the presence of certain psychiatric symptoms can influence whether self-rating or interview-based assessment needs to be used.
22- At the 6-month follow-up, depression did not show a significant response to DBS and its effects on motor and non-motor symptoms.
23- At the 6-month follow-up, there was a worsening of apathy. Assessment of apathy should cover other aspects like social and environmental factors as they are reported to influence the severity of apathy.
24- There is a lack of validated measuring tools specific to PD.
25- A significant reduction in carers' burden was observed.

6.1.3 Summary Points: The Single Site Audit

1- Adding brief, validated scales can improve pre- and post-DBS assessment quality.
2- Scheduling completion of such scales after a DBS operation date is confirmed may assure DBS eligible patients and encourage openness.
3- Such action plan can reduce assessment periods with little burden on clinics.

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Appendices

Appendix 1 – Registered PROSPERO For the Narrative Review

Neuropsychiatric aspects of deep brain stimulation in neurodegenerative disorders: a systematic review

Citation

Arteen Ahmed, Matthew Butler, Paul Shotbolt, Dag Aarsland, Camille Wratten. Neuropsychiatric aspects of deep brain stimulation in neurodegenerative disorders: a systematic review. PROSPERO 2020 CRD42020184000 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020184000

Review question

1- Whether there is an effect of DBS on neuropsychiatric comorbidities (for example, ICDs/cognition/depression/psychosis) in neurodegenerative disorders

2- Whether there is data to suggest optimal DBS parameters to improve or minimise negative effects on neuropsychiatric syndromes of neurodegenerative disorders.

3- Whether DBS offers a viable treatment option for cognitive and behavioural disorders in neurodegenerative disorders (PD, PDD, DLB, Alzheimer's)

Searches

Last Search will be done in PubMed, Ovid/Embase, Ovid/MEDLINE, Ovid/PsycINFO on 30/4/2020

Types of study to be included

Any interventional prospective or retrospective designs (i.e. case-control, cross-sectional, cohort,…)

Condition or domain being studied

Neuropsychiatric disorders

Participants/population

Inclusion: -Include people (any age) with a clinical diagnosis of a neurodegenerative disorder

- Patients with or without Neuropsychiatric syndromes

Exclusion: those with unconfirmed diagnosis, or diagnosis different from neurodegenerative disorders

Intervention(s), exposure(s)

Deep brain stimulation has been used in clinics to treat various neurological diseases including neurodegenerative disorders. In deep brain stimulation (DBS), a specific anatomical target in the brain is stimulated via surgically implanted electrodes. These electrodes produce electrical currents of a specific voltage, wavelength and frequency. The electrodes are connected via subcutaneous wires to an implantable pulse generator (IPG) surgically fixed on the chest wall. After electrodes and IPG are successfully installed, clinicians can adjust and modulate the stimulation via a remote device connected to the IPG to obtain an optimal benefit.

Comparator(s)/control

The control group either

1) Sham treatment (off)

2) Pharmacological treatment.

3) Resective/ lesional surgery.

4) DBS in off-mode.

5) A different DBS site

Context

The languages considered will be English. There will be no restrictions by type of year or setting. We will limit the search to human participants. We will request grey literature from research groups that work on the topic, and we will include unpublished literature, if authors are able to provide enough details for inclusion in the review

Main outcome(s) [1 change]

Changes in the Neuropsychiatric profile of patients pre and post-operation measured by clinical and research neuropsychological tools will be recorded. These include but not limited to depression, apathy, OCD.

Measures of effect

- The risk of developing specific neuropsychiatric symptoms in specific neurodegenerative disorders after undergoing DBS with specific parameters.

- Predictability of development of neuropsychiatric symptoms after DBS in neurodegenerative disorders

- Better candidates for the intervention

- Effect of DBS on neuropsychiatric symptoms (improvement and deterioration)

Additional outcome(s)

None

Measures of effect

None

Data extraction (selection and coding)

A data extraction form developed a priori will be used to summarise data from the selected articles. This has been developed based on the Cochrane Handbook for Systematic Review Checklist of items to consider in data collection or data extraction (Table 7.3.a; Higgins & Green, 2011).

In order to reduce bias and errors in data extraction, this will be carried out independently by two reviewers (AA and MB) / by AA and cross-checked by PS/DA. The extraction form will be piloted on a small number of studies, and adjusted in case any aspects prove not to be adequate or specific enough, before being used on all selected studies.

Study authors might be contacted to request missing information or clarify ambiguities. If impossible to obtain otherwise, means and measures of dispersion will be approximated from figures.

In case any overlapping reports of the same study will be individuated, only the “core” paper containing the key study data will be considered for data extraction, using the other papers as supplements. This will be highlighted in the review text.

Risk of bias (quality) assessment

No studies will be excluded from the review based on their risk of bias or applicability; all relevant evidence will be reviewed and possible reasons for bias or heterogeneity will be discussed. Quality assessment will be carried out after data extraction has been completed, in order to be blind to study quality during data extraction and minimise bias in data reporting.

Studies will be assessed for quality, i.e. “the degree to which a study employs measures to minimise bias and error in its design, conduct and analysis” . This systematic review will adhere to the items of preferential reports for systematic reviews and meta-analyses (PRISMA, Moher et al., 2009), the PRISMA harms checklist and the Cochrane Handbook of Systematic Reviews of Interventions.

Strategy for data synthesis [1 change]

We expect to pool data from numerous studies with heterogenous methodologies, a realist, qualitative synthesis deemed to be pertinent.

Before commencing theming during the data extraction, all included studies will be divided according to NDD, i.e. PD, AD, etc. This is to evaluate outcomes and conditions of interest in the context of specific neurodegenerative disease. Second, under each division, studies will be subdivided according to whether NPS is their primary outcome measure or secondary. Studies with similar methodologies, targets, DBS parameters and subject characteristics will be synthesized together. Themes are repeated implicit ideas across studies, in our case that could include, but not limited to, “feasibility of DBS in patients with NPS” and “role of age in NPS development after DBS”.

These themes are helpful to answer our questions. Each reviewer will independently develop a theme for each extracted study by combining codes which are clearly used in that study. These codes could include, but not limited to, deterioration, improvement, change etc. These codes could be specific to settings of that study, a concept in the study or a characteristic of subjects in the study.

Within themes, findings will be categorized. Each category represents an explicitly described outcome. To illustrate, for example, in feasibility theme mentioned above, while categories can be “positive outcome”, “negative outcomes” and “neutral outcomes”, codes can be safety and effect of DBS. All codes will interactively be refined during the extraction and synthesis process.

Defined questions in the data extraction forms, answered independently by reviewers (AA, MB, CW) and solved for conflicts by PS/DA, will be put next to opposite answers in other studies. Also, findings will be conceptualized based on the circumstances of original studies. Using the same approach, chains of inferences across articles will be sought and linked together in the same theory.

Analysis of subgroups or subsets

Not intended

Contact details for further information

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Organisational affiliation of the review

King's College London, IoPPN

Review team members and their organisational affiliations [1 change]

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Dr Camille Wratten. South London and Maudsley NHS Foundation Trust, OCD, BDD and Related Disorders Clinic, Michael Rutter Centre, Maudsley Hospital, Denmark Hill, London, SE5 8AZ

Type and method of review

Systematic review

Anticipated or actual start date

30 April 2020

Anticipated completion date [1 change]

20 September 2020

Funding sources/sponsors

Self-Funded PhD

Conflicts of interest

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Deep Brain Stimulation; Humans; Neurodegenerative Diseases; Parkinson Disease

Date of registration in PROSPERO

09 July 2020

Date of first submission

04 May 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

09 July 2020

Appendix 2 – Protocol For the Narrative Review

Neuropsychiatric effect of DBS in NDD – Systematic Review Protocol

Protocol structure source: PRISMA-P statement
https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-4-1

Section 1. Administrative information

Item 1a. Title

Neuropsychiatric aspects of deep brain stimulation in neurodegenerative disorders: systematic review protocol

Item 2. Registration

The systematic review protocol was submitted for publication in advance on the International Prospective Register of Systematic Reviews (PROSPERO; National Institute for Health Research & University of York, 2015) (registration number CRD42020184000).

Authors

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Item 3b. Contributions

AA, CW and SS performed the review.
PS and DA reviewed the final protocol and will review the manuscript.

Support

Item 5a. Sources

Project undertaken as part of Arteen's Ahmed's PhD.

Item 5b. Sponsor

Self-funded by Arteen Ahmed as part of PhD

Item 5c. Role of sponsor or funder

N/A

Section 2. Introduction

Item 6. Rationale

Parkinson's disease (PD) is a neurodegenerative disorder more common in the elderly, affecting 1% of people > 60. The characteristic motor symptoms of PD are due to loss of midbrain dopaminergic neurons in substantia nigra. Although PD is considered a movement disorder, psychiatric symptoms (PS) such as depression (1), apathy (2), anxiety (3), behavioural (4) and psychosis (5) constitute core clinical features from the early stages or even precede motor symptoms (6). Psychiatric symptoms in PD tend to be more challenging to cope with or to be managed (7). Compared to general population, depression in PD is more commonly associated with severe anxiety, social withdrawal, irritability and anhedonia (8).

Psychiatric symptoms may co-exist with PD as distinct psychiatric comorbidities. Advanced imaging and post-mortem studies have shown loss of serotonergic, noradrenergic, and adrenergic neurons as a cause of PD related PS (9). Therefore, they can also be a direct result of PD's underlying neurodegenerative pathology. In addition, the psychosocial impact of PD or adverse effects of antiparkinsonian medications can induce psychiatric symptoms (10). In PD-related PS, dopaminergic involvement partly explains the observed improvement of depressive mood and development of psychiatric side effects such as mania, psychosis and impulsivity after dopamine replacement therapy (DRT) (11). Psychiatric side effects of DRT such as impulsivity, apathy and mania can be of significant concern, fuelling the ongoing search for alternative, more efficient and less problematic treatment strategies.

Deep brain stimulation (DBS) is an established treatment for motor symptoms in PD. Although PD patients with severe psychiatric disorders are usually deemed ineligible for DBS, caregivers commonly report psychiatric symptoms like depression, irritability, agitation, anxiety and apathy prior to undergoing DBS surgery (12,13). The relationship between DBS and post-operative psychiatric symptoms is yet to be clearly elucidated. The presence of pre-operative psychiatric disorders, peri-operative factors such as microlesions caused by the invasive surgery and post-operative stimulation are all contributory factors to post-operative psychiatric outcomes (14).

Subthalamic nucleus (STN) and internal globus pallidum (GPi) are the most common targets for DBS in PD; both have significant cognitive and psychological functions, including reward processing (15) . Located medially to internal capsule, anteriorly to thalamus and dorsally to substantial nigra, STN has a regulatory role in movement. It receives inputs from external globus pallidum (GPe) and projects excitatory glutaminergic neurons into GPi to activate its inhibitory GABAergic neurons. Inhibitory GABAergic neurons from GPi project into the thalamus to reduce excitation of thalamus, and subsequently decrease movement (16). Through this indirect pathway, STN plays an important role in preventing unwanted movements. STN also received input from the medial prefrontal cortex, nucleus accumbens, the ventral tegmental area, and the limbic ventral pallidum. The medial tip of the STN projects to the limbic part of the substantia nigra and the ventral tegmental area.

By reducing need for antiparkinsonian medication, DBS may reduce drug-induced psychiatric disorders, such as impulse control disorders (ICDs). In addition, by improving motor symptoms, mood and anxiety may also subsequently improve.

Conversely, DBS is also associated with de novo psychiatric symptoms. DBS-related psychiatric symptoms such as anxiety can start preoperatively due to fear of the invasive procedure or the possibility an unsuccessful outcome (17). Preoperational anxiety can negatively affect performance of patients on preoperative neuropsychological assessments (18,19). Reports also show that depending on stimulation target, development of new psychiatric symptoms such as ICDs and hypomania after DBS therapy is not uncommon (12).
In this review we will look at current literature to understand to what extend the effect and optimization of DBS parameters and targeting has taken psychiatric aspects into consideration. In addition, pre-operative psychiatric symptoms are shown to have predictive potential for motor and non-motor outcomes of DBS therapy (20) (21). We will attempt to further understand the relationship between psychiatric symptoms and post DBS outcomes.

Item 7. Objectives

1- Whether there is an effect of DBS on neuropsychiatric comorbidities (for example, ICDs/cognition/depression/psychosis) in neurodegenerative disorders

2- Whether there is data to suggest optimal DBS parameters to improve or minimise negative effects on neuropsychiatric syndromes of neurodegenerative disorders.

3- Whether DBS offers a viable treatment option for cognitive and behavioural disorders in neurodegenerative disorders (PD, PDD, DLB, Alzheimer's)

Section 3. Methods

Item 8. Eligibility criteria

To be included in the review, studies must meet all of the following inclusion criteria, and none of the exclusion criteria (Table 1):

PICO items	Inclusion criteria	Exclusion criteria
Intervention /exposure	□ DBS (STN/GPi..etc)	□ no DBS
Population	□ Include people (any age) with a clinical diagnosis of parkinson's disease (any type or syndrome)	□ Include people with unconfirmed diagnosis
Comparators	□ A control group is present	
Outcomes	Change in psychiatric symptoms following DBS	No record or report about psychiatric outcomes
Study type	□ Any design	□ Case reports, reviews and audits

Other restrictions	Languages considered will be English. There will be no restrictions by type of year or setting. We will limit the search to human participants.

Table 1. Inclusion and exclusion criteria

Item 9. Information sources

Literature search strategies will be developed using terms related to the neurodegenerative disease, psychiatric symptoms, and cognitive functions. We will search PubMed, Ovid: MedLine/EMBASE/both?, and PsychINFO WebOfScience. Additionally, we will review the references of all included studies to identify further relevant work, and we will scan the reference lists of relevant reviews identified through the search.

Item 10. Search strategy

The search strategy will be created by IF, peer-reviewed by SS, and externally reviewed by a KCL librarian with expertise in systematic review searching. After the PubMed strategy is finalised, it will be adapted to the syntax of other databases. A draft PubMed search strategy is reported in Table 2. Terms in the same column will connected by OR, across columns are connected by AND.

	Intervention/ DBS	**Population/ NDD**	**Focus/ Psychiatric disorders**	**Focus/ Psychiatric disorders**
MESH Indexed	"electrical brain stimulation", "deep brain stimulation"	"neurodegenerative diseases", "Parkinson Disease", "Dementia"	**"Obsessive-Compulsive Disorder", "Compulsive Behavior", "Depressive Disorder, Major", "Depressive Disorder", "Depression", "Apathy","Impulsive Behavior", "Disruptive, Impulse Control, and Conduct Disorders", "Gambling", "Binge-eating disorder", "Hallucinations", "Delusions", "Suicide"[Mesh] OR "Suicide, Attempted","Suicide, Completed"**	"Cognitive Dysfunction" or "Cognition" or "memory disorders" or "Dementia" or "executive functions"
KEYWORDS and Mapped terms	"brain depth stimulation" , "electrical brain stimulation", "deep brain stimulation", "electric stimulation therapy", DBS	"Neurodegenerative Diseases" or "idiopathic parkinson's disease" or "lewy body Parkinson's disease" or "Parkinson's disease" or "dementia" or "lewy body dementia" or	**"Obsessive compulsive disorder" or "compulsive behavior" or ocd or "personality disorder" or depression or apathy or impulsivity or "impulsive behaviors" or "Impulsive control disorder" or icd or "pathological gambling" or gambling or shopping or hypersexuality or "compulsive sexual behavior" or hobbyism or "binge eating disorder" or "eating behavior" or punding or "dopamine dysregulation syndrome" or psychosis or hallucination or delusion or suicide or "suicidal ideation" or anxiety**	Executive dysfunction, Memory deficit, cognitive dysfunction, cognitive impairment, verbal fluency, verbal impairment, non-motor symptoms

*: mapped terms on Ovid/Embase/PsycINFO/Medline where each database may offer different mapped terms for each subject
Search Databases: Pubmed (MeSH + Keyword) + OVID/Embase/PsycINFO/Medline (Mapped terms + keywords)

Study records

Item 11a. Data management

Describe the mechanism(s) that will be used to manage records and data throughout the review

We will use EndNote as bibliographic software.

The number of records resulting from the searches in all selected electronic databases will be recorded. Records will be imported in EndNote, duplicate references will be identified and removed, and the number of duplicate references deleted will be recorded.

Item 11b. Selection process

State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)

The process of article selection will be carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines (Moher et al., 2015). A two stages screening process will be followed. In stage one, titles and abstracts will be independently screened by two reviewers (IF and SS) using the inclusion and exclusion criteria. In stage two, full texts of the potentially eligible articles will be obtained and independently screened by two reviewers (IF and SS) for final inclusion/exclusion. Experts in the topic might be contacted to check that no relevant studies have been missed.

Any disagreements between screeners will be resolved through discussion, and if necessary with third party (PS) arbitration. The authors of original studies will be contacted to resolve any uncertainties. Inter-rater reliability will be calculated.

The following information will be recorded: date each search was carried out; copies of all the search terms used for each specific database; number of references identified by each search; number of duplicates removed; number of references screened based on title and abstract; number of full-text papers screened; number of references excluded at stage two, and reasons for exclusion. Results of the search will be reported using the PRISMA flow diagram.

Item 11c. Data collection process

Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators

A data extraction form developed a priori (see Appendix 1) will be used to summarise data from the selected articles. This has been developed based on the Cochrane Handbook for Systematic Review Checklist of items to consider in data collection or data extraction (Table 7.3.a; Higgins & Green, 2011).

In order to reduce bias and errors in data extraction, this will be carried out independently by two reviewers (IF and SS) / by IF and cross-checked by SS. The extraction form will be piloted on a small number of studies, and adjusted in case any aspects prove not to be adequate or specific enough, before being used on all selected studies.

Study authors might be contacted to request missing information or clarify ambiguities. If impossible to obtain otherwise, means and measures of dispersion will be approximated from figures.
In case any overlapping reports of the same study will be individuated, only the "core" paper containing the key study data will be considered for data extraction, using the other papers as supplements. This will be highlighted in the review text.

Item 12. Data items

A data extraction form developed a priori will be used to summarise data from the selected articles. This has been developed based on the Cochrane Handbook for Systematic Review Checklist of items to consider in data collection or data extraction (Table 7.3.a; Higgins & Green, 2011).

In order to reduce bias and errors in data extraction, this will be carried out independently by two reviewers (AA and MB) / by AA and cross-checked by PS/DA. The extraction form will be piloted on a small number of studies, and adjusted in case any aspects prove not to be adequate or specific enough, before being used on all selected studies.

Study authors might be contacted to request missing information or clarify ambiguities. If impossible to obtain otherwise, means and measures of dispersion will be approximated from figures.

In case any overlapping reports of the same study will be individuated, only the "core" paper containing the key study data will be considered for data extraction, using the other papers as supplements. This will be highlighted in the review text.

Item 13. Outcomes and prioritization

Based on our scopus search, we anticipate that different studies will choose to report group-level differences or individual discrimination indices, or both, depending on the study focus. Prioritization of outcome measures is established based on the framing of the primary systematic review question around *post-DBS effects on psychiatry outcomes.*
The primary outcome will be the effect size of the group-level difference in the post-DBS outcomes measures examined by the selected studies.
Secondary outcome measures will be studies that investigate optimization of DBS parameters for psychiatric outcomes.

Item 14. Risk of bias in individual studies

No studies will be excluded from the review based on their risk of bias or applicability; all relevant evidence will be reviewed and possible reasons for bias or heterogeneity will be discussed. Quality assessment will be carried out after data extraction has been completed, in order to be blind to study quality during data extraction and minimise bias in data reporting.

Studies will be assessed for quality, i.e. "the degree to which a study employs measures to minimise bias and error in its design, conduct and analysis" . This systematic review will adhere to the items of preferential reports for systematic reviews and meta-analyses (PRISMA, Moher et al., 2009), the PRISMA harms checklist and the Cochrane Handbook of Systematic Reviews of Interventions.

Data

Item 15a. Data synthesis

We expect to pool data from numerous studies with heterogenous methodologies, a realist, qualitative synthesis deemed to be pertinent.
Before commencing theming during the data extraction, all included studies will be divided according to NDD, i.e. PD, AD, etc. This is to evaluate outcomes and conditions of interest in the context of specific neurodegenerative disease.
Second, under each division, studies will be subdivided according to whether NPS is their primary outcome measure or secondary. Studies with similar methodologies, targets, DBS parameters and subject characteristics will be synthesized together. Themes are repeated implicit ideas across studies, in our case that could include, but not limited to, "feasibility of DBS in patients with NPS" and "role of age in NPS development after DBS".
These themes are helpful to answer our questions. Each reviewer will independently develop a theme for each extracted study by combining codes which are clearly used in that study. These codes could include, but not limited to, deterioration, improvement, change etc. These codes could be specific to settings of that study, a concept in the study or a characteristic of subjects in the study.
Within themes, findings will be categorized. Each category represents an explicitly described outcome. To illustrate, for example, in feasibility theme mentioned above, while categories can be "positive outcome", "negative outcomes" and "neutral outcomes", codes can be safety and effect of DBS. All codes will interactively be refined during the extraction and synthesis process.
Defined questions in the data extraction forms, answered independently by reviewers (AA, MB, CW) and solved for conflicts by PS/DA, will be put next to opposite answers in other studies. Also, findings will be conceptualized based on the circumstances of original studies. Using the same approach, chains of inferences across articles will be sought and linked together in the same theory.

Item 15b. Summary measures

We do not anticipate being able to run a meta-analysis. However, if data are appropriate for quantitative synthesis, summary measures, and methods of handling and combining data will be established and published on PROSPERO a priori.

Item 15c. Additional analyses

We do not anticipate being able to run any additional quantitative analyses. However, if data are appropriate methods for sensitivity analysis, subgroup analysis, meta-regression etc. will be established and published on PROSPERO a priori.

Item 15d. Type of summary

A qualitative description of the results will also be performed to systematically summarise the characteristics of the included studies and their findings.
Sections will be organised according to what populations were compared

Results of the quality assessment will be described and the potential sources of bias discussed. Sources of heterogeneity between studies will be highlighted.

Item 16. Meta-bias(es)

Selective outcome reporting will be assessed. If the study protocol has been registered or published, this will be examined to assess whether results from all planned measures and outcomes have been reported in the final article. If the study protocol is not available, outcomes reported in the results section will be compared with those reported in the methods.
In order to correct for publication bias, we will include grey literature identified through a "call for grey literature" to relevant research groups.

Item 17. Confidence in cumulative evidence

The confidence in cumulative evidence will be judged based on recommendations outlined in the Grading of Recommendations Assessment, Development and Evaluation (GRADE; Schünemann, 2013). This provides a framework for categorising the strength of the evidence based on the following factors: risk of bias, directness of evidence, consistency and precision of results, risk of publication bias, magnitude of the effect, dose-response gradient, and influence of residual plausible confounding.

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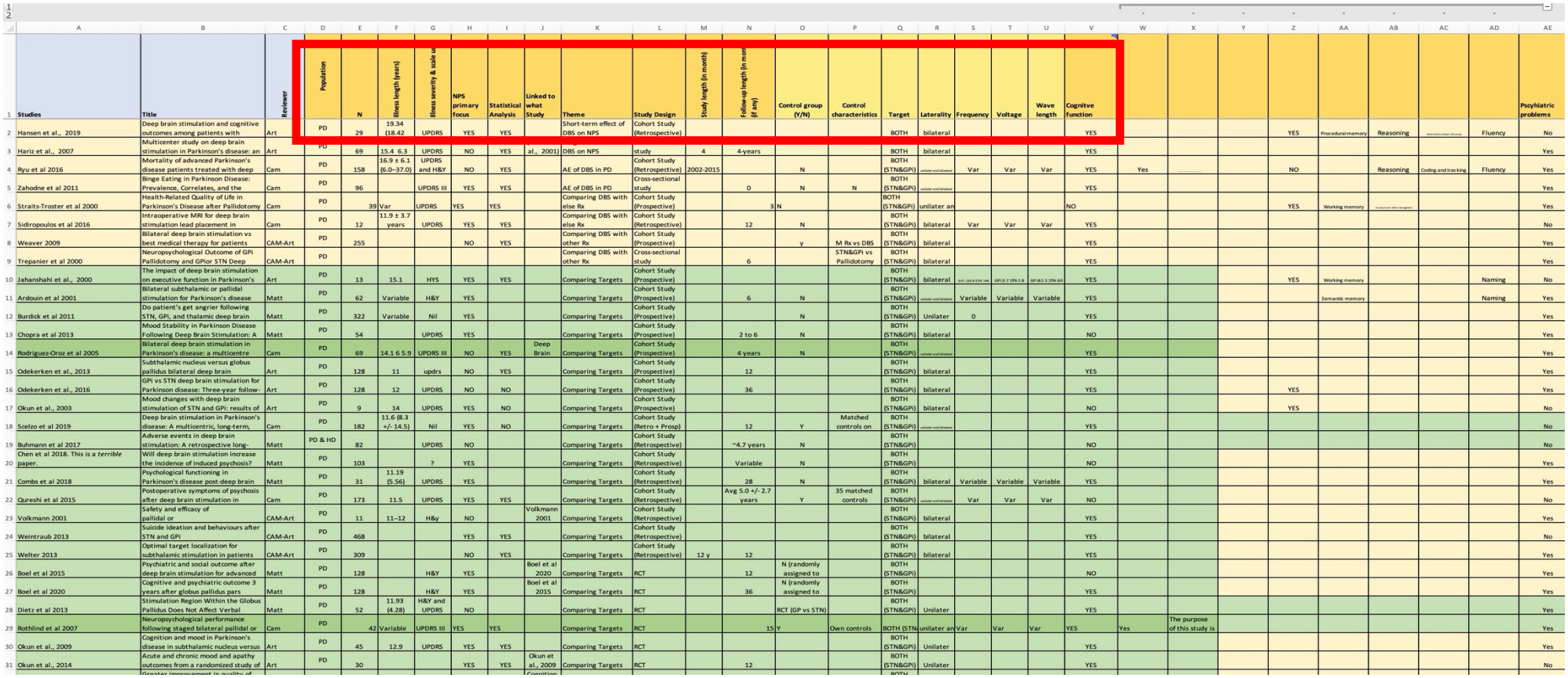
Appendix 3 – Ranking Chart – Narrative Review



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE
1	Studies	Title	Reviewer	Population	N	Illness length (years)	Illness severity & scale us	NPS primary focus	Statistical Analysis	Linked to what Study	Theme	Study Design	Study length (in month)	Follow-up length (in mont (if any)	Control group (Y/N)	Control characteristics	Target	Laterality	Frequency	Voltage	Wave length	Cognitve function									Psychiatric problems
2	Hansen et al., 2019	Deep brain stimulation and cognitive outcomes among patients with	Art	PD	29	19.34 (18.42	UPDRS	YES	YES		Short-term effect of DBS on NPS	Cohort Study (Retrospective)					BOTH	bilateral				YES				YES	Procedural memory	Reasoning		Fluency	No
3	Hariz et al., 2007	Multicenter study on deep brain stimulation in Parkinson's disease: an	Art	PD	69	15.4 6.3	UPDRS	NO	YES	al., 2001)	DBS on NPS	study	4	4-years			BOTH	bilateral				YES									Yes
4	Ryu et al 2016	Mortality of advanced Parkinson's disease patients treated with deep	Cam	PD	158	16.9 ± 6.1 (6.0–37.0)	UPDRS and H&Y	NO	YES		AE of DBS in PD	Cohort Study (Retrospective)	2002-2015		N		BOTH (STN&GPi)	unilater and bilateral	Var	Var	Var	YES	Yes			NO		Reasoning	Coding and tracking	Fluency	Yes
5	Zahodne et al 2011	Binge Eating in Parkinson Disease: Prevalence, Correlates, and the	Cam	PD	96		UPDRS III	YES	YES		AE of DBS in PD	Cross-sectional study		0	N	N	BOTH (STN&GPi)	unilater and bilateral				YES									Yes
6	Straits-Troster et al 2000	Health-Related Quality of Life in Parkinson's Disease after Pallidotomy	Cam	PD	39	Var	UPDRS	YES	YES		Comparing DBS with else Rx	Cohort Study (Prospective)		3	N		BOTH (STN&GPi)	unilater an				NO				YES	Working memory				Yes
7	Sidiropoulos et al 2016	Intraoperative MRI for deep brain stimulation lead placement in	Cam	PD	12	11.9 ± 3.7 years	UPDRS	YES	YES		Comparing DBS with else Rx	Cohort Study (Retrospective)		12	N		BOTH (STN&GPi)	bilateral	Var	Var	Var	YES									No
8	Weaver 2009	Bilateral deep brain stimulation vs best medical therapy for patients	CAM-Art	PD	255			NO	YES		Comparing DBS with other Rx	Cohort Study (Prospective)			y	M Rx vs DBS	BOTH (STN&GPi)	bilateral				YES									Yes
9	Trepanier et al 2000	Neuropsychological Outcome of GPi Pallidotomy and GPior STN Deep	CAM-Art	PD							Comparing DBS with other Rx	Cross-sectional study		6		STN&GPi vs Pallidotomy	BOTH (STN&GPi)	bilateral				YES									Yes
10	Jahanshahi et al., 2000	The impact of deep brain stimulation on executive function in Parkinson's	Art	PD	13	15.1	HYS	YES	YES		Comparing Targets	Cohort Study (Prospective)					BOTH (STN&GPi)	bilateral	GPi: 135.8 STN 146	GPi3.7 STN 2.8	GPi 82.5 STN 60	YES				YES	Working memory			Naming	No
11	Ardouin et al 2001	Bilateral subthalamic or pallidal stimulation for Parkinson's disease	Matt	PD	62	Variable	H&Y	YES			Comparing Targets	Cohort Study (Prospective)		6	N		BOTH (STN&GPi)	unilater and bilateral	Variable	Variable	Variable	YES					Semantic memory			Naming	Yes
12	Burdick et al 2011	Do patient's get angrier following STN, GPi, and thalamic deep brain	Matt	PD	322	Variable	Nil	YES			Comparing Targets	Cohort Study (Prospective)			N		BOTH (STN&GPi)	Unilater	0			YES									Yes
13	Chopra et al 2013	Mood Stability in Parkinson Disease Following Deep Brain Stimulation: A	Matt	PD	54		UPDRS	YES			Comparing Targets	Cohort Study (Prospective)		2 to 6	N		BOTH (STN&GPi)	bilateral				NO									Yes
14	Rodriguez-Oroz et al 2005	Bilateral deep brain stimulation in Parkinson's disease: a multicentre	Cam	PD	69	14.1 6 5.9	UPDRS III	NO	YES	Deep Brain	Comparing Targets	Cohort Study (Prospective)		4 years	N		BOTH (STN&GPi)	unilater and bilateral				YES									Yes
15	Odekerken et al., 2013	Subthalamic nucleus versus globus pallidus bilateral deep brain	Art	PD	128	11	updrs	NO	YES		Comparing Targets	Cohort Study (Prospective)		12			BOTH (STN&GPi)	bilateral				YES									Yes
16	Odekerken et al., 2016	GPi vs STN deep brain stimulation for Parkinson disease: Three-year follow-	Art	PD	128	12	UPDRS	NO	NO		Comparing Targets	Cohort Study (Prospective)		36			BOTH (STN&GPi)	bilateral				YES				YES					Yes
17	Okun et al., 2003	Mood changes with deep brain stimulation of STN and GPi: results of	Art	PD	9	14	UPDRS	YES	NO		Comparing Targets	Cohort Study (Prospective)					BOTH (STN&GPi)	bilateral				NO				YES					No
18	Scelzo et al 2019	Deep brain stimulation in Parkinson's disease: A multicentric, long-term,	Cam	PD	182	11.6 (8.3 +/-14.5)	Nil	YES	NO		Comparing Targets	Cohort Study (Retro + Prosp)		12	Y	Matched controls on	BOTH (STN&GPi)	unilater and bilateral				YES									No
19	Buhmann et al 2017	Adverse events in deep brain stimulation: A retrospective long-	Matt	PD & HD	82		UPDRS	NO			Comparing Targets	Cohort Study (Retrospective)		~4.7 years	N		BOTH (STN&GPi)					NO									No
20	Chen et al 2018. This is a *terrible* paper.	Will deep brain stimulation increase the incidence of induced psychosis?	Matt	PD	103		?	YES			Comparing Targets	Cohort Study (Retrospective)		Variable	N		BOTH (STN&GPi)					NO									Yes
21	Combs et al 2018	Psychological functioning in Parkinson's disease post-deep brain	Matt	PD	31	11.19 (5.56)	UPDRS	YES			Comparing Targets	Cohort Study (Retrospective)		28	N		BOTH (STN&GPi)	bilateral	Variable	Variable	Variable	YES									Yes
22	Qureshi et al 2015	Postoperative symptoms of psychosis after deep brain stimulation in	Cam	PD	173	11.5	UPDRS	YES	YES		Comparing Targets	Cohort Study (Retrospective)		Avg 5.0 +/- 2.7 years	Y	35 matched controls	BOTH (STN&GPi)	unilater and bilateral	Var	Var	Var	NO									No
23	Volkmann 2001	Safety and efficacy of pallidal or	CAM-Art	PD	11	11–12	H&y	NO		Volkmann 2001	Comparing Targets	Cohort Study (Retrospective)					BOTH (STN&GPi)	bilateral				YES									Yes
24	Weintraub 2013	Suicide ideation and behaviours after STN and GPI	CAM-Art	PD	468			YES	YES		Comparing Targets	Cohort Study (Retrospective)					BOTH (STN&GPi)	bilateral				YES									No
25	Welter 2013	Optimal target localization for subthalamic stimulation in patients	CAM-Art	PD	309			NO	YES		Comparing Targets	Cohort Study (Retrospective)	12 y	12			BOTH (STN&GPi)	bilateral				YES									Yes
26	Boel et al 2015	Psychiatric and social outcome after deep brain stimulation for advanced	Matt	PD	128		H&Y	YES		Boel et al 2020	Comparing Targets	RCT		12	N (randomly assigned to		BOTH (STN&GPi)					NO									Yes
27	Boel et al 2020	Cognitive and psychiatric outcome 3 years after globus pallidus pars	Matt	PD	128		H&Y	YES		Boel et al 2015	Comparing Targets	RCT		36	N (randomly assigned to		BOTH (STN&GPi)					YES									Yes
28	Dietz et al 2013	Stimulation Region Within the Globus Pallidus Does Not Affect Verbal	Matt	PD	52	11.93 (4.28)	H&Y and UPDRS	NO			Comparing Targets	RCT			RCT (GP vs STN)		BOTH (STN&GPi)	Unilater				YES									Yes
29	Rothlind et al 2007	Neuropsychological performance following staged bilateral pallidal or	Cam	PD	42	Variable	UPDRS III	YES	YES		Comparing Targets	RCT		15	Y	Own controls	BOTH (STN	unilater an	Var	Var	Var	YES	Yes	The purpose of this study is								Yes
30	Okun et al., 2009	Cognition and mood in Parkinson's disease in subthalamic nucleus versus	Art	PD	45	12.9	UPDRS	YES	YES		Comparing Targets	RCT					BOTH (STN&GPi)	Unilater				YES									Yes
31	Okun et al., 2014	Acute and chronic mood and apathy outcomes from a randomized study of [greater improvement in quality of	Art	PD	30			YES	YES	Okun et al., 2009 [Correction	Comparing Targets	RCT		12			BOTH (STN&GPi)	Unilater				YES									No

Using Excel ordering function, for each section, studies were first organized based on 1- primary focus on the psychiatric symptom, 2-design, 3-cohort size.

Population	N	Illness length (years)	Illness severity & scale used	NPS primary focus	Statistical Analysis	Linked to what Study	Theme	Study Design	Study length (in month)	Follow-up length (in month) (if any)	Control group (Y/N)	Control characteristics

Using Excel ordering function, for each section, ***A closer look at variable used to order studies under each subsection.***

Appendix 4 – Protocol – CRISP Study

Clinical Response of Impulsivity after Brain Stimulation in Parkinson's disease

Which factors are important in predicting changes in Impulse Control Behaviours (ICBs) following Deep Brain Stimulation (DBS) for Parkinson's disease?

Chief Investigator	Dr David Okai e-mail: david.okai@slam.nhs.uk tel: 020 3228 2330 fax:
Sponsor(s)	Mr Dunstan Nicol-Wilson South London and Maudsley NHS Foundation Trust R&D Department Room W1.08 Institute of Psychiatry, Psychology & Neuroscience (IoPPN) De Crespigny Park London SE5 8AF 020 7848 0339 slam-ioppn.research@kcl.ac.uk
Funder (s):	The study has received a grant from Parkinson's UK to complete the study. This is applied to after Dec, 2023.
IRAS Reference	285162

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KEY WORDS
Deep Brain Stimulation, Impulse control disorder, Parkinson's Disease, impulse control behaviours/symptoms

LIST OF ABBREVIATIONS

DBS	Deep Brain Stimulation	***ICBs***	Impulsive Control Behaviours
ICDs	Impulsive Control Disorders	***STN***	Subthalamic Nucleus
PD	Parkinson's Disease	***QUID-RS***	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease -Rating Scale
QUIP	Questionnaire For Impulsive-Compulsive Disorders In Parkinson's Disease	***PICs***	Parkinson's Impulse-Control Scale
NPI	Neuropsychiatric Inventory	***GAD-7***	General anxiety disorder-7
PHQ9	Patient Health Questionnaire-9	***EQ-5D***	EuroQol 5 Dimension
PDQ-39	Parkinson's Disease Questionnaire-39	***CGI-S***	Clinical Global Impression – Severity scale
GGI-I	Clinician's Global Impression – Improvement Scale	***ZCB***	Zarit Caregiver Burden Scale
WSAS	Work And Social Adjustment Scale	***UPPS-P***	Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency
SPSS	Statistical Package For The Social Sciences – Software	***VAS***	visual analogue scale
UPDRS	Unified Parkinson's Disease Rating Scale	***QALY***	Quality-Adjusted Life Year
TEED	Total Electrical Energy Delivered	***DA***	dopamine agonist
NIHR	National Institute For Health Research	***DDS***	Dopamine dysregulation syndrome
DAWS	Dopamine Agonist Withdrawal Syndrome	***CBT***	cognitive behavioural therapy
DSM-IV	Diagnostic And Statistical Manual Of Mental Disorder 4th Edition	***MIDI***	Minnesota Impulsive Disorders interview
QoL	Quality Of Life	***GPi***	Globus Pallidus
ViM	Ventral Intermediate Nucleus Of Thalamus	***STROBE***	The Strengthening the Reporting of Observational Studies in Epidemiology
PI	Principal Investigator	***CI***	Chief Investigator
RF	Research Fellow		

Table 1 – List of abbreviations

1 STUDY SUMMARY

STUDY OVERVIEW	
Full title	What factors are important in predicting changes in Impulse Control Behaviours (ICBs) following Deep Brain Stimulation (DBS) for Parkinson's disease?
Acronym	CRISP
Secondary Title	Multicentre Observational Study of Impulsive Behaviours following Deep Brain Stimulation in Parkinson's Disease
Objectives	The objective of this prospective observational cohort study is to answer the following clinically important questions: 1. In patients with a pre-operative history of ICBs, what is the likelihood of improvement or deterioration in ICBs post-operatively? 2. What is the risk of developing post-operative de novo ICBs after Subthalamic Nucleus DBS (STN DBS)? 3. What factors are important in predicting changes in ICBs after STN DBS? 4. What is the impact of ICBs on carer's quality of life QoL and burden?
Type of trial	Observational Study
Trial design and methods	The study will record outcomes related to ICBs for PD patients who have already been selected for DBS therapy as a routine clinical treatment in participating DBS operating centre It is routine practice to assess ICBs before DBS decisions are made, but the manner varies across DBS operating centres. The only additional factor to the routine DBS clinical pathway in this study is that the centres involved will perform assessments in a uniform manner to allow data to be combined. A set of clinical assessment scales for ICBs, as well as other relevant neuropsychiatric symptom assessment will be added to routine pre- and post- operational clinical assessments for participants. The primary endpoint of the study is the change in severity of ICBs. Patients who score positive on the QUIP will then have two further scales validated for use of assessment of Impulse control behaviours ICBs – the patient-rated QUIP-RS and clinician-rated (performed by AA) PICs). Other questionnaires to be administered are listed below: 1. Neuropsychiatric Inventory (NPI) 2. General anxiety disorder-7 (GAD-7) 3. Patient Health Questionnaire-9 (PHQ9) 4. Parkinson's disease questionnaire-39 (PDQ-39) 5. EuroQol 5 Dimension (EQ-5D) 6. Clinical Global Impression – Severity scale (CGI-S) at baseline and Clinician's Global Impression – Improvement scale (GGI-I) post-operatively. 7. Zarit Caregiver Burden Scale

	8. Work and Social Adjustment Scale 9. UPPS-P Impulsive Behaviour Scale 10. Apathy Evaluation Scale 11. The Snaith-Hamilton Pleasure Scale Assessments will be performed at baseline, 3, 6 and 12 months post-operatively. Results will be analysed to ascertain potential predictive measures for ICBs development/change.
Health condition(s) or problem(s) studied	Impulse Control Behaviours in Parkinson's disease on the routine DBS clinical care pathway.
Target sample size	Consecutive recruitment for 12 months from the operating centres for PD patients who ARE selected to have DBS for the motor complications of PD (this is routine treatment). We anticipate 50-100 patients depending on number of sites involved.
Observation duration per participant:	~ 13 months
Main inclusion/exclusion criteria:	All participants will have already been selected for DBS to treat their motor symptoms, as part of their routine care, by their treating DBS team in their centre. Only English-speaking patients will be eligible.
Statistical methodology and analysis:	Descriptive analysis will be run for ICBs among our cohort, at baseline and all follow ups. Repeated measure analysis will be used to measure significance of change in outcome of interest over time. We will examine the factors predicting a change in the QUIP-RS after DBS. Multiple linear regression will be used to predict a change in QUIP-RS and PICs between pre-operative scores and 12-month postoperative scores. Primary Predictors in the model will include age, sex, baseline QUID-RS score, Target nucleus of DBS if different nuclei are routinely targeted, Total Electrical Energy Delivered (TEED), Reduction in Dopamine agonist only dose, reduction in levodopa only dose and changes in Levodopa Equivalent daily dose (LEDD) (this is a total amalgamated dose) following DBS. The following secondary analyses will be performed. 1. A detailed qualitative and quantitative analysis of factors predicting changes in the QUIP-RS and PICs questionnaire following surgery, targeted only at those participants who have or develop significant (as judged by the routine clinical team managing their pre and post-operative care) ICBs during the study. 2. Multiple regression analyses to explore factors influencing caregiver burden and quality of life (EQ-5D, and Zarit) after DBS. 3. Investigation of whether individual DBS settings or lead position influence ICBs. Numbers are expected to be small and so these will only be explored in those who have significant ICBs

	4. Qualitative analysis to investigate trends in changes in QUIP-RS questionnaire over 12 months.
STUDY TIMELINES	
Study Duration/length	~ 48 months
Expected Start Date	Aim for August 10th 2021
End of Study definition and anticipated date	~ June 1st, 2025
Key Study milestones	Start date • The first patient will be recruited as soon as ethical approval is granted. Submission • The study will be submitted for publication within three years of first recruitment. Budget • The UK DBS registry is already active. The database does not require extra funding to cover the additional cost of incorporating the research components, as this only involves addition of research questionnaires into the registry. • A research fellow RF (AA) has been enrolled as PhD candidate in order to ensure the research assessments are being correctly performed and data collected uniformly across the multiple centres. • The RF will be trained by senior clinicians (DO/PS) in the application of rating scales and is already registered for a PhD at King's College London.
STORAGE of SAMPLES (if applicable)	
Human tissue samples	N/A
Data collected / Storage	A local investigator at each participating centre will collect, record and store documents in a designated locker at the local centre. The record will be transferred to an online database provided by Orion company.The Research team at IoPPN will be granted access to this database by Orion. All data related to this study will be accessible from a designated and password protected computer at IoPPN main building and hard copy of all relevant documents will be saved in a designated locker at same place. Only AA and DO will have access to both database and lockers.

2 Participating centres from the UK National UK DBS Network

All participating neurologist, neurosurgeons, neuropsychiatrists, DBS nurses will be named on any presentation or publication

Centre	Principle investigator	Secretary Phone number	E-mail
NHS Glasgow and Clyde -Glasgow	Dr Edward Newman	0141 201 2478	Edward.Newman@ggc.scot.nhs.uk
King's College Hospital NHS Foundation Trust - London	Dr Paul Shotbolt	0207 848 0962	paul.shotbolt@kcl.ac.uk
The Walton Centre - Liverpool	Dr Antonella Macerollo	07776813575	Antonella.macerollo@thewaltoncentre.nhs.uk
Newcastle upon Tyne Hospitals NHS Foundation Trust - Newcastle	Mrs Una Brechany	*0191 282 9317*	una.brechany@nuth.nhs.uk
Oxford University Hospitals NHS Foundation Trust - Oxford	Dr Raj Sarangmat	07912145463	nagaraja.sarangmat@ouh.nhs.uk
Barking Havering and Redbridge University Hospitals NHS Trust	Dr Anjum Misbahuddin	07950777793	anjum.misbahuddin@nhs.net
Salford Royal NHS Foundation - Salford	Dr Monty Silverdale	0161 206 2574	Monty.Silverdale@manchester.ac.uk
Addenbrooke's Hospital– Cambridge	Dr Valerie Voon		vv247@cam.ac.uk

Table 2 Participating DBS centers

3 INTRODUCTION

In January 2014, the UK DBS Network was formed from the Parkinson's Disease Clinical Studies Group (then under National Institute for Health Research NIHR) to share best practice, collect information, and facilitate research across all DBS centres in the UK. Members of the group are all consultant neurologists, neurosurgeons, neuropsychiatrist, specialist nurses and academics from 17 DBS implanting centres. The network is supported by the Parkinson's Excellence Network. It meets every six months or yearly. The first initiative was to create a database of essential clinical data including age, sex, UPDRS, information on surgery, targets, device information, QoL and complications on up to 300 DBS cases a year across the UK. DBS surgery is routinely funded as part of standard care by NHS England (1). During the first 6 months of the registry, 84 entries were made (up to Jan 2017). The UK DBS Network has identified the need and the opportunity to add a specific research component to this database, the cost of which is not covered by NHS England. If every UK DBS centre collaborating in the Network contributes, it can recruit a large number of consecutive patients who have undergone DBS creating a large and valuable DBS research resource, presenting deliverable DBS research opportunities for the UK. The first proposed study addresses the relationship of ICBs with subthalamic nucleus (STN) DBS.

Over a decade ago, it was recognised that the interaction of ICBs and DBS would be complex, when members of our group asked, "is pathological gambling an indication or a contra-indication for DBS?"(2). Since then, studies attempting to address this question have produced inconsistent results, and so we now wish to use the large data pool of UK DBS patients and our national collaboration to address this important and common question, as it is faced in DBS clinics regularly (3).

4 BACKGROUND AND RATIONALE

Why is this project important?

Impulse Control Disorder and Impulse Control Behaviour in Parkinson's

Impulse Control Disorders (ICDs) are defined as behaviours that are performed repetitively, excessively and compulsively to an extent that these behaviours interfere negatively in activities of daily living of patients and their carers (4). ICDs together with other related impulsive and compulsive behaviours are collectively referred to as Impulsive Control Behaviours ICBs (5). ICBs all share a repetitive, reward, or incentive-base nature.

There are 4 major ICDs in PD:

1. Pathological Gambling
2. Compulsive Buying

3. Compulsive Sexual Behaviour
4. Compulsive Eating Behaviour (6,7)

Other common related ICBs in PD include: Dopamine dysregulation syndrome (DDS), a drug addiction-like state associated with self-medicating with inappropriately high doses of PD medication, in particular levodopa (8), punding - repetitive purposeless behaviours such as collecting or rearranging objects (9), hobbyism - similar but higher level than punding such as excessive artwork and hoarding - the acquisition of and failure to discard objects (10). In recent years, there has been increasing evidence and awareness regarding the frequency of ICBs in Parkinson's disease (PD). ICBs are often unreported by patients and unrecognized in routine assessments. Consequently, unnoticed ICBs can have a catastrophic deleterious effect on the financial, social and relationship status of patients and carers over time (11). A study of 3,090 PD patients in North America found a prevalence of severe ICBs in 13.6% of PD patients which is high when compared to the background population rate of around 5%. More recently, in a multicentre longitudinal cohort study in PD patients (n=411), after 5 years of follow up, the prevalence of ICBs among the cohort increased from 19.7% at baseline to 32.8%(12). Reportedly, a very high percentage of patients without a formal ICB diagnosis can test positive on the QUIP (5), but this is not sufficient to assess ICBs in the routine clinical care(6). To elaborate, QUIP, is a screening tool that screens only for urges or thoughts of an impulsive behaviour which has been linked to dorsal striatum system, whereas execution of that behaviour (ICB) is linked to ventral striatum system in the brain (13). A semi structure interview like QUIP-RS and PICs, can produce more details by investigating beyond the urge and assessing the severity and social impacts of impulsive behaviours not only the urge.
ICBs are strongly associated with DA use (7,14). Independent associations are reported between lifetime average DA daily dose and duration of treatment with ICBs severity (12)(6). Other factors associated with ICBs include:

1. younger age; male sex; early onset PD; being unmarried; current cigarette smoking; a personal or family history of gambling or alcoholism; impulsive or novelty seeking traits (6,14).
2. Several psychiatric symptoms are more common in PD patients with ICB, including anxiety, depression and sleep disturbance (6,15) (work from our group).
3. The incidence of ICBs in untreated PD is very similar to control therefore ICBs are felt to be a side effect of treatment, in particular dopamine agonist treatment, rather than a manifestation of PD per se (7).
4. ICBs in PD are associated with decreased quality of life (16) and increased caregiver burden(15).
5. ICBs are frequently seen in DBS clinics (16 %) because patients being considered of DBS typically have tried high dose medication, may be younger and may be seeking high levels of quality-of-life improvements (3,17)

None of the published studies have statistically analysed the factors which might predict changes in ICBs post DBS. The lack of consistent evidence means that at present DBS clinicians are not clear on precisely how to counsel patients as to whether DBS could improve or worsen ICBs, when they co-exist with motor fluctuations / dyskinesias (which are the indications for DBS), as they commonly do (18,19). This multicentre observational study will be a pragmatic "real-world" study to evaluate symptoms of ICBs and other neuropsychological aspects including mood, quality of life, personality, social activity etc. in detail before and after DBS, identifying factors that are important in predicting or determining whether ICBs will improve or worsen post DBS. This study, by measuring ICBs, and correlating them to the factors mentioned in below, will enable clinicians to directly answer this question, leading to improved patients counselling in movement disorder clinics.

DBS and ICBs relationships

DBS is only indicated for movement symptoms in PD, and so by using DBS to control parkinsonian motor symptoms, it is hypothesised that the drug-induced side effects associated with dopaminergic medication could be reduced because post-operative drug reduction usually is the norm after STN DBS. There is an evolving hypothesis which suggests that if medication (in particular dopamine agonist therapy) is reduced following DBS, then ICBs may improve, although there is concern that apathy and other symptoms of dopamine agonists withdrawal syndrome DAWS might then develop post-operatively (20–22). On the one hand, there has been interest in the potential use of DBS to aid in the treatment of PD patients with established ICBs (20), in particular targeting the subthalamic nucleus (STN)(18,23,24). There is also a great deal of scientific evidence suggesting that the subthalamic nucleus is important in delaying motor responses and reducing impulsive behaviour (25,26). Not all ICBs respond to DBS similarly, for example, pathological gambling is reported to have a better response to DBS than other reported ICBs (27).
On the other hand, STN DBS in itself might potentially worsen impulsivity through a direct effect on STN function induced by electrical stimulation of the intended target or surrounding structures. Overall, it is likely that multiple different factors may potentially be important in predicting changes in ICBs following surgery, including predisposing factors (in particular sex, age and symptoms of ICBs preceding surgery), operative factors (target), and postoperative factors (medication changes, stimulator settings). Published studies into the effect of DBS on ICBs have been case reports and case series. Furthermore, these published studies have focused on the presence (yes.no) of ICBs, with little information on the assessment of severity (changes in frequency/intensity/impact). The results from the studies have been very mixed, with some studies demonstrating worsening ICBs after DBS and other studies demonstrating improvement (21,28–30). In summary, the current data are conflicting.

Treatment of ICBs

There is a paucity of evidence-based data to guide the management of ICBs in PD (31). Current practice is to reduce or withdraw dopamine agonist medication which will usually

lead to an improvement or resolution of ICBs (17) (review from our group).
However, a proportion of symptoms can persist, and some patients are unable to tolerate medication reduction. Medication withdrawal is associated with two potential complications: firstly, some patients are likely to develop worsening motor symptoms (as the motor state is now treated less); secondly some patients may develop dopamine agonist withdrawal syndrome (DAWS), which is a neuropsychiatric syndrome akin to substance misuse withdrawal, characterised by symptoms including anxiety, apathy, depression and diaphoresis (3)(32). Similar to other psychostimulant withdrawal syndromes, DAWS is consistent with the lack of response to levodopa, antidepressants and anxiolytics and the improvement with DA replacement. Atypical antipsychotic medications are sometimes added to a patient's drugs to improve ICBs but there is very little evidence base to guide this treatment. Other trials of medical therapies showed unproven benefit (33)(31). Only one randomized trial of cognitive behavioural therapy CBT from our group was shown to help some aspects in some cases (17,34).

ICBs scales

Lack of unified criteria has affected the study of risk factors and prognosis of ICBs in Parkinson's disease(5). Although, there are several validated rating scales available to measure ICBs. These scales can be divided into those that are used as screening tool and allow a dichotomous outcome (Yes, No) or categorical outcomes, which assess the presence or absence of ICBs, and those which grade the severity of ICBs. Screening scales include DSM-IV screening, the Questionnaire for Impulsive Compulsive Disorders in PD (QUIP) and the Minnesota Impulsive Disorders interview MIDI (5,6,35,36). The Ardouin scale is a semi-structured interview which documents what are termed "hypo-dopaminergic" behaviours including apathy and depression as well as "hyper-dopaminergic" behaviours, including ICBs (37). Ardouin scale completion takes up to one hour making it less practical time wise in studies such as this one in which multiple scales will be used (38). Other more practical quantitative scales allow us to follow up ICBs over time, and to measure small changes in ICBs rather than simply documenting the presence or absence of severe ICBs. Quantitative measures include: -

1) The validated QUIP-RS (Questionnaire for Impulse Control Disorder in Parkinson's disease – Rating Scale) (39). This is a brief scale, completed by the patient, documenting impulsivity symptoms including pathological gambling, hypersexuality, compulsive shopping and compulsive eating. Very little training is required to be able to administer this scale. QUIP-RS is an adapted form of Questionnaire for Impulsive-Compulsive Disorder in Parkinson's disease (QUIP) which constituted of 3 sections: the first section screens for 4 ICBs (gambling, eating, sexual and buying behaviours), the second section screens for other compulsive behaviours (punding, walkabouts and hobbyism) and the third section screens for compulsive medication use (36). A group from the International Parkinson's disease and Movement disorder society (MDS) who performed an assessment for all available ICBs scales, has classified QUIP-RS as a 'recommended' scale for making diagnosis (exc. DDS)

and assessing severity of ICBs (5). Of note, QUIP-RS does not measure ICBs impact on social life of patients. In addition, the QUIP-RS scale, however, does not provide sufficient detail to fully explore many aspects of ICBs that may be apparent on clinical interview (for instance many of the qualitative factors, such as predisposing, precipitating and maintaining factors)

2) The PICs (Parkinson's Impulse Control Scale) (39), on the other hand, is a more detailed scale (devised and validated by our group) that additionally covers each impulsive aspect, including punding, hobbyism, and dopamine dysregulation syndrome. PICs is a clinician-rated scale based on a semi-structured interview that measures both the intensity of each ICB (indicated by frequency and scale of the behaviour) and its individual social impact, indexing severity with more precision (39). Training is required to administer this scale and is included in our proposal. The PICs has been classified within 'suggested' scales by the MDS group (5). This means that although it has been validated to make a diagnosis and to assess severity and social impact of ICBs in PD. This study can add further clinimetric data to its use.

We will be able to detect a larger number of patients with mild ICBs efficiently and quantify the presence of ICBs by using a low threshold on QUIP-RS. Participants scoring above one for any ICBs on QUIP-RS, will therefore be also assessed with RF-rated PICs, which is capable of assessing ICB's in more detail. This two-stage approach will enable us to capture as many patients with +ICBs as possible in the study and importantly also to target resources most efficiently towards those with the most significant symptoms. Those who do not score positive on the QUIP at baseline will fill out the scale in the next follow up, in addition to other neuropsychological scales, to detect any change or development of ICBs.

Using quantitative scales will therefore enable a more detailed study of ICBs and other potential neuropsychological aspects. The results of this study, which will be published, can guide clinicians when counselling PD patients with and without impulsivity, before DBS. It will therefore directly influence clinical care nationally. Furthermore, members of our study team have extensive expertise in ICBs and in DBS, with 7 peer-reviewed publications presented here, and so are in an excellent position to deliver results from this study and subsequently disseminate its findings to the Parkinson's community.

We wish to answer the following clinically important questions:

1) What is the risk of developing post-operative de novo ICB's after STN DBS?

2) In patients with a pre-operative history of ICBs, what is the likelihood of improvement or deterioration in ICBs post-operatively?
3) Which factors are important in predicting changes in ICBs after STN DBS?

4) What is the impact of ICBs on carer's quality of life and burden?

5 OBJECTIVES

5.1 Primary Objectives

a) Descriptive analysis of post-DBS changes in mild ICBs that were deemed to be suitable to proceed to surgery.
b) Descriptive analysis of recurrence of ICBs post-DBS in those with history of ICBs using scores on QUIP-RS/PICs
c) Descriptive analysis of de novo cases of ICBs post-DBS

5.2 Secondary Objectives

What are predictive factors for de novo, recurrence and change in severity of ICBs described above (a, b, and c)?
How does the change in ICB relate to QoL (EQ-5D) for patients (using PDQ39 and EQ-5D)?
How does the change in ICB relate to QoL for the carer, measured by Zarit and EQ-5D?
How does change in ICBs relate to changes in other measured psychiatric aspects?
How does change in ICBs relate to change in personality traits measured by an ICBs specific personality test (UPPS-P Impulsive Behaviour Scale)?

6 Methodology

6.1 Study setting

Currently, there are seventeen DBS centres in the UK, of which seven centres have agreed to cooperate and participate in this study. All potential participants will have been selected by their clinicians for DBS to treat their motor symptoms as a routine clinical care. They will be approached during their hospital appointment by their clinical care team, who will be the research link to this study, principal investigator (table 2, page 4). All patients selected for DBS at each centre will be given an introductory package either by post or in person at the clinic. The introductory package will contain:

1. Introductory Instruction sheet
2. Study Information sheet (one for patient, one for carer)
3. Two Consent forms (one for patient and one for a carer)
4. Self-rated questionnaires (T0) to be completed (patient and carer) before activation of the stimulation, if participated
5. Prepaid Royal Mail return envelope addressed to RF (AA) address at KCL/ IoPPN

The protocol for this study will be written according to STROBE guidelines and will be published on Clinicaltrials.org. In addition, Dr Okai from South London and Maudsley Trust (SLaM) will take role of chief investigator and SLaM will be sponsor of the study. The study is coordinated by research fellow (AA) a PhD student registered at KCL/IOPPN.

6.2 Experimental design

This is a multicentre prospective observational cohort study that will examine ICBs changes among PD patients after undergoing deep brain stimulation (DBS) up to 12 months after the surgery. The study is designed to add only a small number of questionnaires to participants' clinical follow-up during study, with minimal burden for patients and the health team. Most participants will have STN DBS. Routine clinical care sometimes includes Globus Pallidum GPi or ventral intermediate nucleus of thalamus ViM DBS, but these are rarer than STN DBS. We will record data on all DBS operations across seven participating centres listed in Table 2, and if there is enough GPi or ViM DBS cases, they will be analysed as parallel subgroups.

6.3 Study time points and Timeline

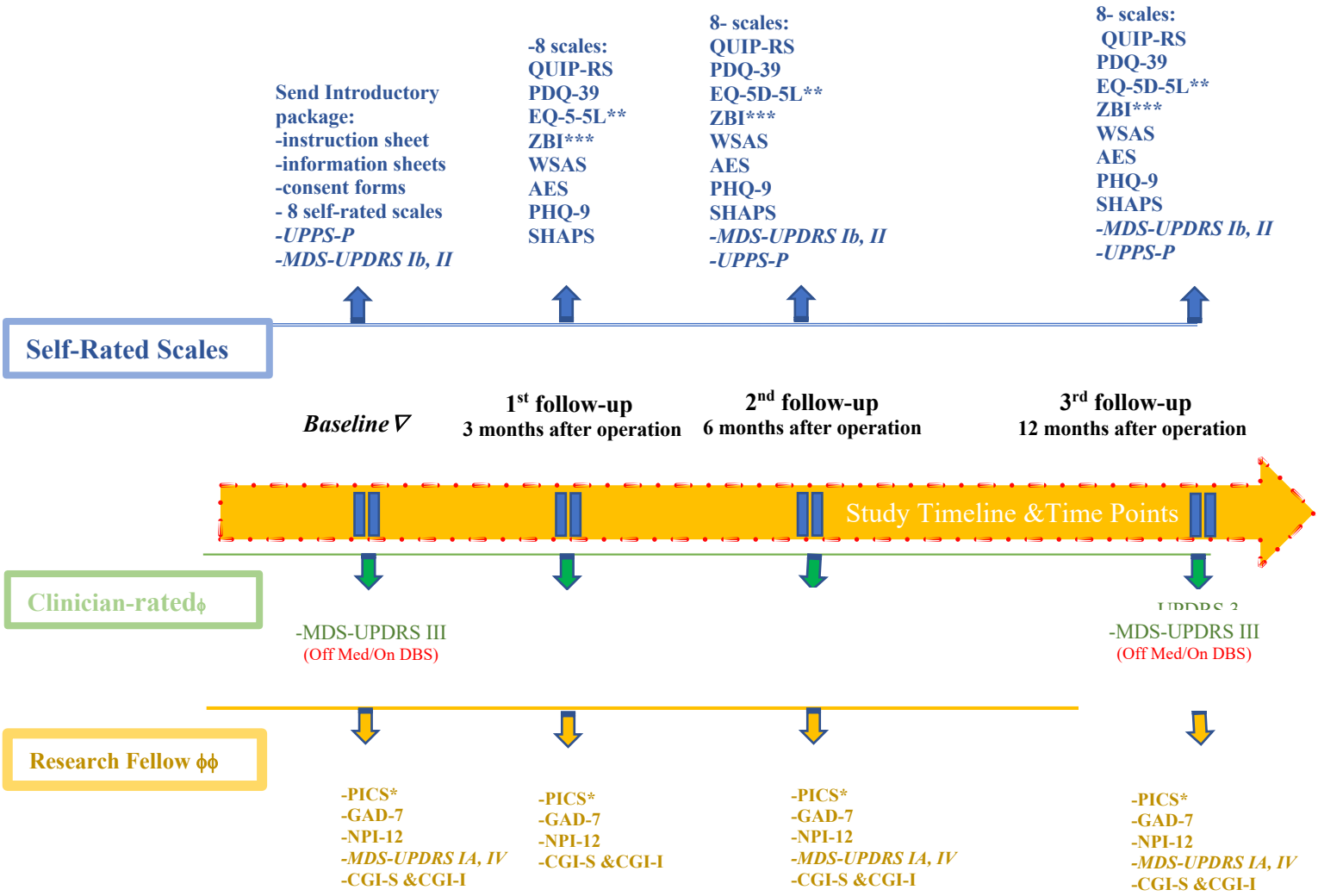

Figure. 1 Timeline of research scales

*Pics will be done only those who score above 1 on QUIP-RS

**EQ-5D is completed by both carer and patient measuring their quality of life separately

*** This is completed by carer only

ϕ to be done by local principal investigators in the clinic

ϕϕ to be done by RF over phone

	Data Collection			*Administration*			*Permission of use*	
	Clinical core	*Research Scales*	*Time point*	*By whom*	*Time*	*location*	*Conditions*	*Status*
Demography (Age, sex, Ethnicity)	√		Baseline	Clinic. Care Team	-	At local Clinic	Ethics required	
PD duration	√		Baseline	Clinic. Care Team	-	At local Clinic	Ethics required	
DBS TARGET	√		Baseline	Clinic. Care Team	-	At local Clinic	Ethics required	
DBS Parameters *	√		0-, 3-, 6-, 12-month time	Clinic. Care Team	-	At local Clinic	Ethics required	
Tabulated Medication Box		√	0-, 3-, 6-, 12-month time	Clinic. Care Team	-	At local Clinic	Ethics required	
MDS-UPDRS PART 3	√		0-, 12-month time	Clinic. Care Team	-	At local Clinic	Ethics required	
MDS UPDRS PARTS 1, 2, 4	√		0-, 6-, 12-month time	Research Fellow (AA)	10 mins	Over Phone	Ethics required	
QUIP-RS		√	0-, 3-, 6-, 12-month time	Self-administered	3 mins	At home	Required (Free of charge)	√
AES		√	0-, 3-, 6-, 12-month time	Self-administered	10 min	At home	Not Required	
SHAPS		√	0-, 3-, 6-, 12-month time	Self-administered	10 mins	At home	Not required	
PICs ϕ		√	0-, 3-, 6-, 12-month time	Research Fellow (AA)	10 mins	Over Phone	Required (Free of charge)	√
PDQ-39	√		0-, 3-, 6-, 12-month time	Self-administered	~ 15 mins	At home	required (Free of charge)	√
EQ-5D (patient + Carer)	√		0-, 3-, 6-, 12-month time	Self-administered	3 mins	At home	Required (free of charge)	√
NPI		√	0-, 3-, 6-, 12-month time	Research Fellow (AA)	5 mins	Over Phone	Required (Free of charge)	√
GAD 7		√	0-, 3-, 6-, 12-month time	Research Fellow (AA)	2 mins	Over Phone	Not Required	√
PHQ-9		√	0-, 3-, 6-, 12-month time	Self-administered	2 mins	At home	Not Required	√
CGI-S		√	0-, 3-, 6-, 12-month time	Research Fellow (AA)	2 mins	Over Phone	Not Required	√
CGI-I		√	0-, 3-, 6-, 12-month time	Research Fellow (AA)	2 mins	Over Phone	Not Required	√
ZBI - Carer		√	0-, 3-, 6-, 12-month time	Self- administered	10 mins	At home	Required (Free of charge)	√
WSAS		√	0-, 3-, 6-, 12-month time	Self-administered	3 mins	At home	Not Required	√
UPPS-P		√	0-, 6- 12-month time	Self- administered	20 min	At home	Not required	√

Table 3

*: *DBS parameters include mA or volts, pulse width, frequency, contacts impedance, TEED and directionality if available*

ϕ: *This will be done in each follow up only for those who score above 1 an any give questions on QUIP-RS*

DBS candidates will be approached by clinician to inform them about this study and get their verbal agreement to be contacted by RF (through phone, email, and post), if interested. Regarding details of data collection, candidates then will be formally invited to join the study through a post mail which will contain the introductory package. In the included instruction sheet, there will be clear instructions how to go through the introductory package. Firstly, they will have to read the comprehensive information sheet in which participants are provided with a phone number and e-mail address to contact for any query. In the information sheet they will be provided with full information about what this study is about, how participants will be involved, risks and benefits of joining the study and more. If they decide to join the study, they will need to sign carers and patients consent form and fill out the attached self-rated scales in the introductory package.

The clinical core data and completed research scales will be transferred by each participating centre's principal investigator and RF, respectively, into an online database provided by third party company, Orion MedTech. Orion MedTech is responsible for providing the online database (at no cost) for all participating centres. The RF will be responsible for entering the data. The CI and RF will have access to the clinical core data, in addition to the research component scales during study.

The research component scales, are shown in Table 3; four of these added scales are administered by the RF over phone. Upon receipt, participants can complete all other six self-administered scales enclosed in the introductory package. Participants will be recommended to complete the QUIP-RS in presence of a family member/carer/partner, and to make a note on the QUIP-RS sheet whenever there is disagreement between patients and carers regarding ratings given to any of questions on QUIP-RS. Ratings above 1 (from 0-4) to any of questions on QUIP-RS, and/or having a dispute over rating with the carer/partner/family member, will automatically trigger the administration of Parkinson's Impulsive Control scale (PICs). The PICs scale therefore will only be administered for those patients who have rated one or more questions on the QUIP-RS >1 or/and whose family member/carer/partner would rate one or more questions differently to the patient. As shown in the study schedule (Table 1), patients will be approached by our RF to administer PICs and other clinician rated scales at **baseline** (i.e., 6 weeks before operation until postoperatively before activation of the stimulation), **three**, **six** and **twelve** months after the surgery. Finally, those who do not score above 1 on any of the questions in QUIP-RS nor have any rating disagreements with carers will be given the QUIP-RS again at the next clinical follow-ups to detect any changes in ICBs. Carers will also be invited to take part in this study to investigate impact of ICBs and DBS on their quality of life. For this, carers will be invited to complete two scales, as shown in table 3.

As mentioned above, the research component will constitute of an additional set of scales that assess predictors and risk factors that are hypothesised to relate to changes in ICBs. These will be a mixture of patient-rated and clinician-rated scales.

The following additional rating scales will also be performed by the local PI or RF or patient/carer themselves, as shown in figure 1, and entered into the registry by PI and RF:

1. Questionnaire for Impulsive-Compulsive Disorder in Parkinson's disease Rating Scale (QUIP-RS) by using a 5-point Likert scoring that measures frequency and severity of ICBs (39).
2. Parkinson's Impulsive Compulsive scale (PICs)
3. The Neuropsychiatric Inventory (NPI) will be administered to assess patients for presence and severity of comorbid psychiatric disorder (41). It is administered by RF to an informed caregiver, preferably one who lives with the participant.
4. GAD7 is clinician rated and PHQ-9 is a self-administered diagnostic instrument which assess anxiety and depression and take about 2 and up to 10 minutes to complete, respectively (42,43).

5. The CGI-S and the CGI-I will be administered to give a clinician-rated global measure of ICBs baseline severity and post-DBS change (44,45). Both should not take more than 2 minutes combined.
6. The Zarit Burden scale is a self-administered (by carer) scale to measure carer burden (15)(46). This scale will be administered to the carer as long as there is a carer who consents to be involved in the study. Otherwise, this assessment will be omitted.
7. Quality of life QoL will be measured using the EQ-5D (paper version) and PDQ-39 (47,48). While both are self-completed reports, the former takes only few minutes, and the latter takes about 15-20 minutes. Carers will also be invited to fill one EQ-5D copy for themselves.
8. The MDS-UPDRS (49) will be measured to provide a comprehensive measure of motor symptoms of PD. Part I, II, IV will be administered at baseline, 6 , 12 months after the surgery. Part III will be administered by specialist nurses at baseline and after 12 months.
9. AES (50) and SHAPS (51) measure apathy and anhedonia, respectively. Although both apathy and anhedonia will be measured briefly by other scales in this study, AES and SHAPS will help us investigate them as separate psychiatric symptoms and will allow us to examine their association with QoL and other measured psychiatric aspects.
10. Work and Social Adjustment Scale (WSAS) (52) is a self-report scale which will measure impairment in functioning (takes 2 minutes to complete).
11. UPPS-P Impulsive Behaviour Scale is self-report scale is a multifaceted and multidimensional scale reflecting four impulsive personality traits: (i) Negative urgency: tendency to act rashly under extreme negative emotions, (ii) Lack of Premeditation: tendency to act without thinking, (iii) Lack of Perseverance: inability to remain focused on a task, (iv) Sensation Seeking: tendency to seek out novel and thrilling experiences (v) Positive urgency: tendency to act rashly under extreme positive emotions(53)

All scales (exc. UPDRS and UPPS-P) will be completed at baseline (pre-operatively), 3 months, 6 months, and 12 months postoperatively (table. 3). Self-administered scales will be sent out and followed-up by RF personally by sending email, call or mail periodically. Any clinical concerns raised by this research component will be fed back to the responsible local clinician.

	Recruit.	***Baseline** (From 6 weeks before operation, until before activation (programming) of the implanted stimulating device)*	***After 3 months***	***After 6 months***	***After 12 months***
Visit No	-1	0	1	2	3
Window of flexibility for timing of visits:	1 month	3 wks.			
Informed Consent	*				

DBS Parameters		*	*	*	*
Medical History		*			
Eligibility confirmation	*	*			
Routine Pre-operative neuropsychological and neuropsychiatric assessment		*			*
QUIP-RS		*	*	*	*
PICs		*↓↓	*↓↓	*↓↓	*↓↓
MDS-UPDRS (all Parts)		*		*!	*
PHQ-9		*	*	*	*
GAD-7		*	*	*	*
NPI		*	*	*	*
PDQ-39		*	*	*	*
EQ-5D		*	*	*	*
CGI-S		*	*	*	*
CGI-I		*	*	*	*
Zarit Burden interview		*	*	*	*
AES		*	*	*	*
SHAPS		*	*	*	*
UPPS-P		*		*	*
Adverse Events Review			*	*	*
Concomitant Medication Review i) Agonist dose (ii) Levodopa dose (iii) Total LEDD dose (iv) other relevant drugs, MAOI, Entacapone, etc	*	*	*	*	*

Table 4. Study schedule

↓↓ PICs will be done only for those who score above (1) on any question of QUIP-RS or/and whose answer to questions has conflict with that of their carer/partner

! This is only for UPDRS I,II, IV

6.4 Eligibility criteria

For Patients

Inclusion criteria:

- Eligible and selected for DBS to treat motor symptoms of Parkinson's disease
- English language fluency

Exclusion Criteria

- Nil

For carers

Inclusion criteria:

- Someone who lives or/and looks after the patient
- English language fluency

Exclusion Criteria

- Nil

6.5 Data management

As shown in the figure 2, after ethical approval is obtained, the collected data will be entered onto an online database provided by Orion MedTech. In addition, Orion will grant us access to the DBS Registry. The principle investigator and RF may keep a anonymised copy of the data on a password KCL/IoPPN computer. Details of data handling will be according to Orion's data sharing agreement with participating centres and the sponsor, SLaM. A team from all neurologists, neuropsychiatrist and specialist nurses from all centres will help in transferring and maintaining the core clinical data under supervision of local investigator of each site.

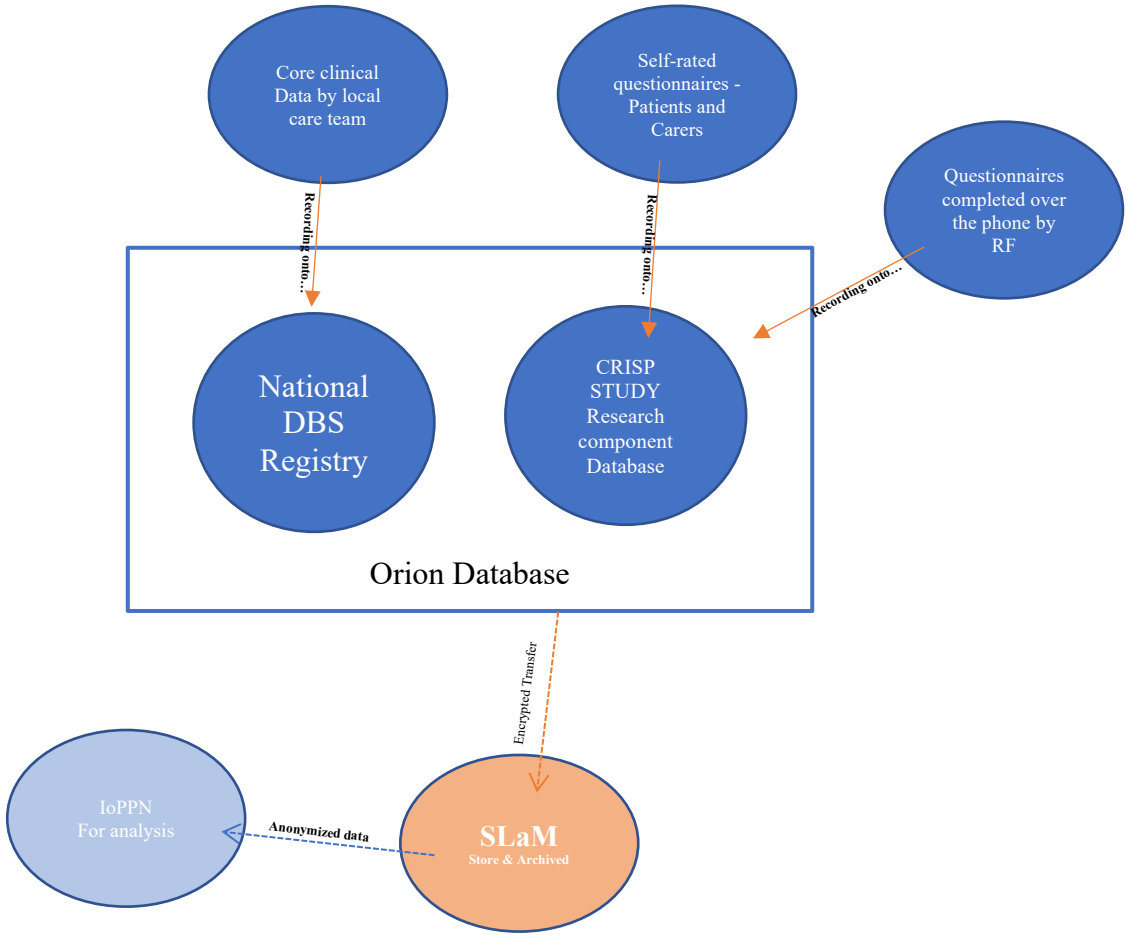

Figure 2 Data management

6.6 Sample size

We expect to recruit around 100 participants across the six participating centres. Of this group, based on prevalence estimates from the literature, 20-25 % will have a history of ICBs, have current mild ICBs or present with de novo ICBs at some point during the study. Our sample size will only contain a small number of participants who either have or develop formally diagnosed ICBs. However, a larger number will either have or develop minor impulsive symptoms which will be detected by changes in the QUIP-RS. We will analyse our data as a case series if we recruit 40 – 60 patients. However, even if we do achieve lower numbers (e.g., say 40 consecutive patients), these will be from 7 sites and so we will be able to provide multi-centred data on this difficult topic suitable for pragmatic patient counselling in DBS clinics. In previously published large trials of DBS (state PDSURG and other trials (7)and large non-trial cohorts, ICBs were not specifically studied. If we recruit 100 participants as expected, this will therefore give us an 80% power to detect a medium effect size on our primary outcome measure (PICs) (f^2=0.15) for the effect of 7 individual predictors (page 20) at a significance level of 5%.

6.7 Statistical analysis plan

All statistical analysis will be performed using SPSS software. Before commencing data analysis, a complete statistical analysis plan will be created. Informed reasons for opting out will be recorded. In this study we are concerned about the risk of inadequate power, therefore we will try not to use complete case analysis when dealing with missing data. Except for ICBs related data we expect all missing data to be missing completely at random. Nevertheless, the reason for missing data for each questionnaire (self-rated and clinician rated) at each follow up will be identified and based on the result appropriate approach will be taken.

In observational study, data from all variables could go missing and that will probably affect validity of data. Among participants with active ICBs, a substantial number of participants may be reluctant to report their symptoms. In order to keep maximum statistical power, apart from dropping out for any reason which is inevitable, data collection and management plan will be designed appropriately to reduce possibility of having missing data such as:

1- Stringent yet practical visit schedule
2- Reminder of late collection or upcoming follow up both for centres and participants
3- RF will timely follow up each participant to ensure required data has been collected and entered into the registry.
4- Regular well-timed meetings between chief investigator and RF with each local investigator regarding follow up and data collection
5- Timely following up on participants whose self-rated questionnaire have not returned in time (real-world report window)
6- Stringent and clear plan for data collection and management

We intend to summarize all characteristics using a descriptive analysis at baseline. We intend to use Shapiro-Wilk test and visual inspection of histograms to examine normality of

distribution. Tests mentioned here are based on the assumption that distribution is normal, if not, non-parametric test will be used.

To understand the mental status, general health status, demographics, and stimulation parameters of our participants we will primarily run a descriptive analysis. As for impulsivity and compulsivity, QUIP will produce nominal variable, i.e., scoring (+) or (-) for previous or current ICB(s). In addition, those who report one and who report more than one ICBs on QUIP-RS will also be recorded in a dichotomous variable (Multi ICBs).

At baseline (T0), using Pearson Chi-square test (if assumptions are met) positivity and severity for ICB (QUIP-RS and PICs) will be tested across the pre-defined age group, gender and multi ICBs variable. Furthermore, separate quantitative and qualitative analysis will be conducted for each reported ICBs on QUIP-RS and PICs. The same test will be performed to analyse neuropsychiatric symptoms like depression (PHQ-8), anxiety (GAD-7), quality of life (PDQ-39 and its domains & EQ-5D-Patient [QALY, utility index and VAS]), social adjustment (WSAS), other neuropsychiatric symptoms (NPI and its domain) and Personality trait (UPPS-P) among ICB +/- populations (QUIP +/-), multi ICBs, gender and age groups will be analysed. At this point, the same examination will be performed for some of these scales' subscales, hence, based on type of variable, a different test will be used. Using an appropriate test, theoretically possible associations between all variables will be tested, such as anxiety and ICBs, depression and quality of life, and so on. This is also to avoid multicollinearity issues when running the multiple regression analysis. Using a multivariate regression model, the relationship between ICBs, as measured by QUIP-RS and PICS, and other potential predictors, listed below, will be analysed.

In next follow-ups (T1, T2, T3), using two paired sample t-test will be used to find any change in ICBs in QUIP-RS and PICs. Same test will be performed for other neuropsychiatric symptoms, quality of life and carer's burden (ZBI &EQ-5D-carer). For subscales, depending on assumptions, appropriate test will be used to seek change over time. Repeated measure ANOVA test will be used for categorical variables. Bonferroni corrections of the significance level will be adopted to account for multiple comparisons. Appropriate tests will be conducted to find confounders and mediation between our independent variables (age, gender, parameters, depression, anxiety etc.) and dependent variable (ICBs).

Our primary outcome of interest (ICBs change on the PICs) is a continuous numerical variable, therefore, multiple linear regression will be used to predict a change in PICs between pre-operative scores and 12-month postoperative scores. To do that first we will test the safety of our regression model using scatterplot on SPSS to see if all assumptions are met. The potential predictors in the model will include the following: -

1- Age. Young age is a recognised risk factor for ICB (6)
2- Sex. Male sex is a recognised risk factor for ICB (6)
3- Baseline QUIP-RS score. In order to determine whether the presence or severity of ICB prior to DBS predicts a worsening or an improvement in ICB following DBS.
4- Target. STN stimulation has been associated with impulsivity (26). Thus, bilateral internal Globus Pallidus (GPi) or ViM stimulation may be less likely to worsen ICB. We will only be able to analyse this factor if we recruit enough participants having GPi or ViM DBS. DBS target will be based on usual practice at the centre.

5- Total Electrical Energy Delivered (TEED) based on final DBS settings. In order to determine whether high DBS settings predict a worsening of ICBs. TEED can be easily calculated from the formula: (Voltage squared x Pulse Width x Frequency) / Impedance (54). By using TEED in this pragmatic approach, we will be able to compare DBS settings across centres that may use different Pulse Width, Frequency and Amplitude settings.
6- Reduction in dopamine agonist dose following DBS. It is recognised that dopamine agonist use is the most important factor causing ICBs in PD patients (6). Thus, it is felt that reduction in dopamine agonist dose is the main factor predicting improvement in ICBs following DBS.
7- Reduction in levodopa dose. Importantly, it is less well recognised that levodopa use also causes ICBs in PD (6,55). Thus, it is felt that reduction in levodopa dose will also predict improvement in ICBs following DBS. However, this has never been formally assessed. Finally, reduction of levodopa equivalent dose (LED) will be calculated and analysed
8- A more detailed qualitative and quantitative analysis of factors predicting changes in the PICs scale following surgery. This analysis will be targeted only to those who have or develop significant ICBs at some point during the study as only those participants will receive the PICs scale. Thus, this analysis will be more targeted. As per published literature, we predict 10-20 % of participants will have PICs applied, so enabling subgroup analysis of 15-20 patients over 12 months recruitment.
9- If trends allow, we will investigate to determine whether individual DBS settings (frequency, pulse width and voltage) have an effect on ICBs which has not been picked up in the TEED analysis.
10- We will perform qualitative analysis to investigate trends in the progression of changes in the QUIP-RS scale, measured every 3 months after surgery. Although the "final outcome" (at 12 months) of DBS will be most important to patient and health care providers, it is recognised that ICBs can transiently deteriorate after DBS, during phases of drug / DBS adjustments (usually < 6 months). The purpose of the multiple assessments at 3, and 6 months is to attempt to delineate the time course and severity of change. This information is considered crucial in counselling patients fully.
11- Assessing any change in personality scores (using UPPS-P) pre- and post-operation, associations with change in ICBs' intensity and social impact.
12- Assessing change in mood and psychotic symptoms among patients with and without ICBs

7 PATIENT AND PUBLIC INVOLVEMENT (PPI)

This research was reviewed by a team with experience of mental health problems and their carers who have been specially trained to advise on research proposals and documentation

through the Feasibility and Acceptability Support Team for Researchers (FAST-R): a free, confidential service in England provided by the National Institute for Health Research Maudsley Biomedical Research Centre via King's College London and South London and Maudsley NHS Foundation Trust
We have also presented the study to a PD lay advisory group, comprised of patients and carers linked with the DBS UK network. We have also discussed the study with several expert patients at King's, who are part of a local support group. We have met with Parkinson's UK (the main UK patient charity) and shared the protocol with them, taking on board any comments. The study has also been shared with all the UK national DBS network, including those centres not recruiting patients. We plan to engage with Parkinson's UK for assessment of study results, discussion, and dissemination of findings.

8 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the SLaM R&I Office and deemed sufficient to cover the requirements of the study.

1) The UK DBS registry is already active. The database company (Orion) will not require extra funding to cover the costs of the research database.

2) A research assistant is employed to follow up and apply questionnaires, only in those scoring above threshold. The research assistant will be trained by the senior staff in the application of rating scales and register for a self-funded PhD, i.e., no extra budget is needed.

9 DATA HANDLING AND MANAGEMENT

The local principal investigator (PI) at each site will be responsible for archiving all research data in an assigned cabinet and will allow the research team to have access to it at any time. All data will also be electronically entered into a central database (Orion) via participating centres' password-protected computers, as shown in figure 2 . Local data governance will apply as per their sites' policies and will be in accordance with national standard research practice. This applies to paper and electronic records, including emails. Electronic research data will be stored on a backed-up server, password protected and accessible only to the research team upon request.

The Orion database is hosted by Orion MedTech Ltd CIC and will store clinical and demographic data for the study within the established national registry for Deep Brain Stimulation (DBS). Orion MedTech has data sharing agreements in place with all study sites as part of the DBS registry which cover submission and storage of patient demographics, and a study-specific data transfer agreement will also be put in place to cover the bespoke study dataset which is not part of the DBS registry. Orion will grant access to study data to the

research team who will be able to download this via encrypted connection for further analysis. The body of data which is specified and consensual in the protocol will be transferred from Orion's database to the designated computer at the SLaM which is protected by a password known only to the chief investigator and research fellow. Furthermore, to be able to contact subjects for phone interview arrangement will need to have access to personal addresses, postcodes, emails or telephone numbers. The intended use of the personal information is only to make contact with research participants in order to conduct interviews. Such information will not be shared with any third parties. Participants will be informed about our data protection measures in the consent form, and information sheet. All stored and publishable data will be anonymised.

10 PEER AND REGULATORY REVIEW

This study has been peer reviewed by expert outside of research team and organization. HRA and NHS REC will review for regulatory approval.

11 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

The CI and R&I Office should be notified immediately of any case where the above definition applies during the study conduct phase.

12 MONITORING AND AUDITING

The Chief Investigator will be responsible for the ongoing management of the study. The Sponsor will monitor and conduct audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the UK Policy Framework for Health and Social Care 2017 and in accordance with the Sponsor's monitoring and audit procedures.

13 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files. The research assistant will be trained by the senior staff in the application of rating scales and register for a PhD.

14 INTELLECTUAL PROPERTY

All intellectual property rights and know-how in the protocol and in the results arising directly from the study but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to SLaM. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to SLaM and to disclose all such know-how to SLaM with the understanding that they may use know-how gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of SLaM confidential information or infringement of SLaM IPR.

15 INDEMNITY ARRANGEMENTS

SLaM NHS Indemnity holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that a participating centre has been negligent. Each site covers any negligence from their staff as part of the conduct policy at their site.

16 ARCHIVING

Local archiving.

The local principal investigator (PI) at each site will be responsible for archiving all research data in an assigned cabinet and will allow the research team to have access to it at any time. All data will also be electronically entered into a central database (Orion), which is an established, secure national registry for the Deep Brain Stimulation (DBS) Network. The Orion database is hosted by Orion MedTech Ltd CIC and will store clinical and demographic

data for the study within the established DBS national registry. Data entry will be via participating centres' password-protected computers, or by the RF. Orion MedTech has data sharing agreements in place with all study sites as part of the DBS registry which cover submission and storage of patient demographics, and a study-specific data transfer agreement will also be put in place to cover the bespoke study dataset which is not part of the DBS registry. Orion will grant access to study data to the research team who will be able to download this via encrypted connection for further analysis.

Local data governance will apply as per their sites' policies and will be in accordance with national standard research practice. This applies to paper and electronic records, including emails. Electronic research data will be stored on a backed-up server, password protected and accessible only to the research team upon request. The body of data which is specified and consensual in the protocol will be transferred from Orion's database to the designated computer at the SLaM which is protected by a password known only to the Chief Investigator and RF. Furthermore, to be able to contact subjects for phone interview arrangement will need to have access to personal addresses, postcodes, emails, or telephone numbers. The intended use of the personal information is only to contact research participants to conduct interviews. Such information will not be shared with any third parties. Participants will be informed about our data protection measures in the consent form, and information sheet. All stored and publishable data will be anonymised.

All data acquired for this study will be stored only on SLaM computers and destroyed after 5 years.

17 PUBLICATION AND DISSEMINATION POLICY

The results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. Results will be published as soon as sufficient data is collected and analysed. The aim is to publish results after sufficient data from all participants is collected at minimum 3-month follow up. If enough number of participants were not recruited, results will be published as case series. Local PIs will present results at local academic and clinical meetings, as well as at UK DBS Network meetings.

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19 APPENDICES

Appendix 1: PROTOCOL VERSIONS

Versions No	Version Date	Status
1.0	15-03-2021	
2.0	14-03-2022	
3.0		**Current**

Appendix 5 – Patient & Carer Information Sheet – CRISP Study

Clinical Response of Impulsivity after Brain Stimulation in Parkinson's disease (CRISP)

Which factors are important in predicting changes in Impulse Control Behaviours (ICBs) following Deep Brain Stimulation (DBS) for patients with Parkinson's?

South London and Maudsley NHS Foundation Trust
Institute of Psychiatry, Psychology & Neuroscience (IoPPN)
De Crespigny Park
London SE5 8AF

Chief Investigator
Dr David Okai
Consultant Neuropsychiatrist
Email: david.okai@slam.nhs.uk

Participant Information Sheet

Patient

You are invited to take part in a research study. Before you decide it is important for you to understand why the research is being done.
Please take the time to read the information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

Who is conducting this study?

The study is being conducted by researchers at the South London and Maudsley NHS Foundation Trust (SLaM). It is part of an educational project and has been approved by the National Research Ethical Committee (ref no: **21/LO/0580**)

What is the purpose of the study?

We wish to carry out a study of the factors that might predict a complication of Parkinson's disease (PD) known as impulse control behaviours (ICBs), in patients who undergo deep brain stimulation surgery (DBS). These ICBs can affect a significant minority of PD patients and lead to them gambling or shopping excessively. They may also develop a change in their sex drive or eating habits.

To do this we will need to see as many people who are due to have DBS before they have had their surgery, and then contact them again at certain time points after their surgery. The aim of the study is to develop a way to measure how severe such problems are, after surgery so that we can develop greater understanding and treatments. The study will involve an assessment by a doctor who has knowledge of PD and such problems.
Therefore, it is a worthy contribution to improve clinical care for Parkinson's patients undergoing DBS therapy on a national level.

Why have I been invited to participate?

You have been invited to participate in the CRISP study because you are a candidate for deep brain stimulation surgery for motor symptoms of Parkinson's disease.

Do I have to take part?

No. Participation in this study is voluntary and you can decide whether to take part. You can have as much time as you like before reaching a decision and will need to have the information sheet for at least 24 hours before reaching a decision. You can let us know of your decision anytime from the time of receiving this package up to one week before your scheduled DBS operation. This is to make sure we have enough time to schedule a phone interview at your convenience before your operation. Not participating in this study WILL NOT have any effect on your clinical care in any way. After deciding to participate, you can withdraw at any time. Through contact details provided below [page 5], you can inform us of your decision to withdraw from this study after participation or inform us if you want us to stop collecting your data from NHS DBS registry and also to let us know if you don't want us to use your collected information after you withdraw.

What will happen to me if I take part?

Should you decide to take part;

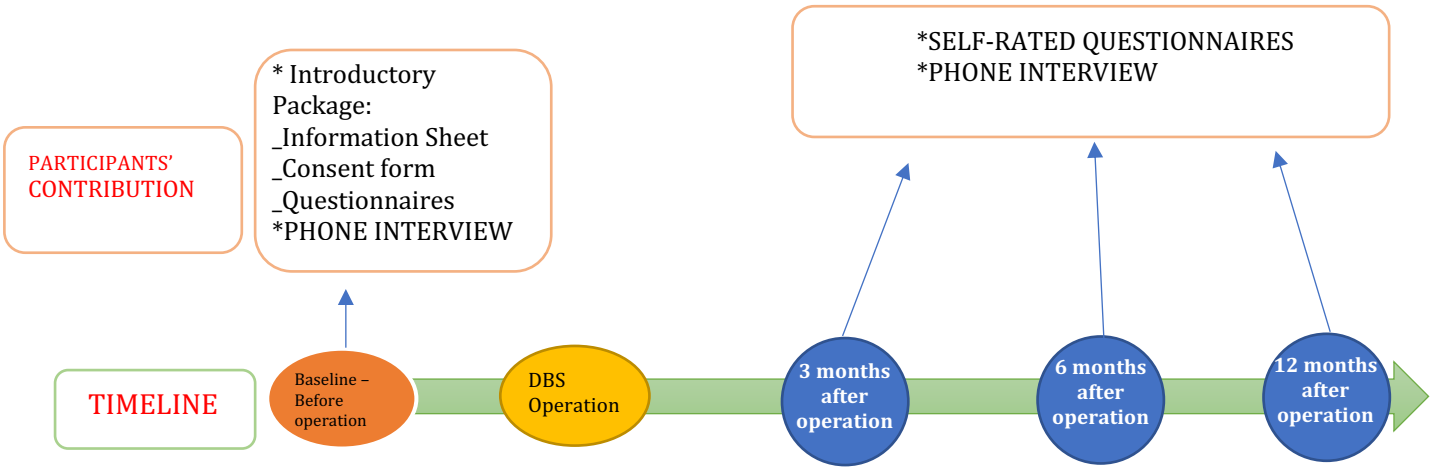
***1)*- We will access your relevant clinical data on the NHS DBS registry**
This will help us analyse the relationship between clinical information, such as age, medication, or DBS settings, with the effect that DBS surgery might have on ICBs and related problems.

Clinical Data to be accessed:

- **Your demographic data** *such as name, gender, age, ethnicity*
- **your relevant medical and drug history** *such as Parkinson's disease duration, deep brains stimulation target & parameters and medications.*

***2)*- You will be invited to complete** 9 questionnaires at home. This will be once before the DBS operation and three times over a course of 12 months after the DBS operation (3,6 and 12 months). Please, look at figure. 1 (page 3) which is an illustration of study's timeline and schedules.
You will also be invited to be interviewed over the phone once before operation, and three times over a course of 12 months after your DBS operation. All the questionnaires you need to complete by yourself will be sent to you by mail, although we are available to help if you have any questions or difficulties. Phone Interviews will be conducted by our research fellow (PhD Student) and will be arranged at a time to suit you.
We estimate that it will take less than an hour to complete the questionnaires sent in the post. Interviews that our research fellow will conduct over the phone should not take longer than 40 minutes in total. During the interviews you will be reminded to take a rest or stop whenever you need to.
Involvement in the study does not replace your normal care and it is expected that you will continue to see your PD Nurse Specialist, GP and Neurologist as normal.

Figure 1. Study schedule AND timeline



Will I be paid if I take part in this study?

Unfortunately, we are not able to offer you any payment to take part in the study.

What are the potential benefits of taking part?

We cannot promise that taking part in the study will benefit you. However, we do hope that your participation may help us to treat future patients with complications of Parkinson's disease better and help us understand the condition in a clinical and research setting.

What are the possible disadvantages of taking part?

The main disadvantage of taking part is the time and effort that it will take.
It is also possible that discussing personal issues can sometimes be upsetting and embarrassing. The doctor and nurse will be as sensitive as possible to your feelings and will not in any way expect you to talk about such matters unless you are willing to do so.

What if something goes wrong?

By participating in this research, you are automatically covered by SLaM NHS Indemnity. If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [insert Principal Investigator name, telephone number and e-mail address LOCAL PI DETAILS ADDED BY SITE]. If you remain unhappy and wish to complain formally, you can do this through the **SLaM Patient Advice and Liaison Service (PALS) on 0800 731 2864 (Option 2) or by email pals@slam.nhs.uk**. If there is still a concern, you can contact Gill Dale, Director of Research Quality at slam-ioppn.research@kcl.ac.uk

Will taking part in this study be kept confidential?

Yes. All information about your participation in this study will be kept confidential. The procedures for handling, storing, and destroying data are compliant with the Data Protection Act 2018. Data about you will be linked to a number rather than a name in order to maintain your anonymity. Information about you will be stored securely and will be available only to members of the research team. Data from this study will be retained for 5 years and then disposed of securely.

What happens if the research team finds abnormalities?

Any incidental finding such as worsening of impulsive behaviours, developing other psychiatric symptoms or other clinical concern raised by this research component will be fed back to the clinician responsible for your health care.

What will happen if I don't want to continue with the study?

You are free to change your mind at any time and decide to withdraw from the study. You don't need to give us any reason for this. Withdrawing from the study will not influence your clinical care in any way. We will retain and continue to use any information you have contributed to the research up to that time, unless you request that we don't use it.

What happens after the study ends?

The results of the study will be published in scientific journals and might be presented at national or international conferences. The data collected from you will be anonymised (it will not be possible to identify you by these data) and safely stored at South London and Maudsley. All data will be destroyed after 5 years.

How will we use information about you?

We will use your clinical data including demographics (age, gender, ethnicity), medical, surgical history, and DBS information. We will also need to use information from the questionnaires you completed by yourself and interviews (over phones). All your information will be anonymised and stored on a fully secure database online via an encrypted connection. Data will also be archived at South London and Maudsley building. To do analysis, all data will be transferred to King's College London anonymised, meaning you will not be identified because your data will have a code number instead. We will keep

all information about you, anonymised, safe, and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are my choices about how my information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- If you choose to stop taking part in the study, we would like to continue collecting information about your health from [central NHS records]. If you do not want this to happen, tell us and we will stop.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can I find out more about how my information is used?

- You can find out more about how we use your information at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by ringing us on [**07490853030**].
- by contacting South London and Maudsley dataprotectionoffice@slam.nhs.uk

Who has reviewed the study?

The West London Research Ethics Committee has reviewed the study for compliance with medical and ethical standards and for scientific value.

Further information and contact details

If you have any questions about the research, your rights as a participant, you would like to report any problem arising from the research, or communicate your decision about withdrawing from the study, please contact any one of the following researchers:

Contact Details for Further information

If you would like to discuss your potential involvement in this research please contact:
Dr Arteen Ahmed on 07490853030
alternatively email: arteen.ahmed@kcl.ac.uk

Thank you for considering your participation in this Study.

Clinical Response of Impulsivity after Brain Stimulation in Parkinson's disease (CRISP)

Which factors are important in predicting changes in Impulse Control Behaviours (ICBs) following Deep Brain Stimulation (DBS) for patients with Parkinson's?

South London and Maudsley NHS Foundation Trust
Institute of Psychiatry, Psychology & Neuroscience (IoPPN)
De Crespigny Park
London SE5 8AF

Chief Investigator
Dr David Okai
Consultant Neuropsychiatrist
Email: david.okai@slam.nhs.uk

Participant Information Sheet

Carer

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The study is being conducted by researchers at the South London and Maudsley NHS Foundation Trust (SLaM). It is part of an educational project and has been approved by the National Research Ethical Committee (ref no: **21/LO/0580**)

What is the purpose of the study?

We wish to carry out a study to investigate the effects of deep brain stimulation on impulse control behaviours (ICBs) and other psychiatric symptoms. These ICBs can affect a significant minority of PD patients and lead to them gambling or shopping excessively. They may also develop a change in their sex drive or eating habits.

As a secondary goal, we would also like to investigate effects of deep brain stimulation (DBS) on carers' quality of life and burden.
To do this we will need to see as many carers of people who are due to have DBS before they have had their surgery, and then contact them again at certain time points after the surgery.

Why have I been invited to participate?

You are invited to participate in this study as a carer of a relative/family member with Parkinson's who is undergoing deep brain stimulation operation. This is to investigate the impact of the deep brain stimulation therapy on your quality of life and burden. You will be eligible to participate only if your relative/family member who is undergoing DBS surgery decides to participate as well.

Do I have to take part?

No. Participation in the study is voluntary and you can decide whether or not to take part. You can have as much time as you like before reaching a decision and will need to have the information sheet for at least 24 hours before reaching a decision. Not participating in this study WILL NOT have any effect on the clinical care of your relative/family member who is undergoing DBS operation. Through contact details provided below [page 5], you can inform us of your decision to withdraw from this study any time after participation or let us know if you don't want us to use your collected information.

What would taking part involve?

If you decide to take part, you will be asked to complete two self-rated questionnaires at home. This will be once before your relative/family member's DBS operation, and three times (3,6 and 12 months) after the DBS operation.

Both questionnaires will be sent to you by mail in the same package as your relative/family member who is undergoing DBS operation. You will find your questionnaires in an envelope labelled as "Self-rated Questionnaires/Carer".

You will have 1 week to complete and the return your self-rated questionnaires with the rest of questionnaires completed by your relative/family member who has also decided to participate in this study. There will be adequate time to complete the questionnaires. The time needed for you to complete both questionnaires is estimated to be less than 15 minutes.

Will I be paid if I take part in this study?

Unfortunately, we are not able to offer you any payment to take part in the study.

What are the potential benefits of taking part?

We cannot promise that taking part in the study will benefit you. However, an advantage of participating as the caregiver of a Parkinson's disease patient who is undergoing DBS surgery may be to improve the clinician's understanding of the way DBS affects you as a carer in terms of carer's burden and quality of life.

What are the possible disadvantage of taking part?

The main disadvantage of taking part is the time and effort it will take. There are no significant risks associated with the completing questionnaires.

What if something goes wrong?

By participating in this research, you are automatically covered by SLaM NHS Indemnity. If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [insert Principal Investigator name, telephone number and e-mail address LOCAL PI DETAILS ADDED BY SITE]. If you remain unhappy and wish to complain formally, you can do this through the **SLaM Patient Advice and Liaison Service (PALS) on 0800 731 2864 (Option 2) or by email pals@slam.nhs.uk**. If there is still a concern, you can contact Gill Dale, Director of Research Quality at slam-ioppn.research@kcl.ac.uk

In the event that something does go wrong, and you are harmed during the research you may have grounds for legal action for compensation against SLaM NHS Foundation Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will taking part in this study be kept confidential?

Yes. All information about your participation in this study will be kept confidential. The procedures for handling, storing, and destroying data are compliant with the Data Protection Act 2018. Data about you will be linked to a number rather than a name in order to maintain your anonymity. Information about you will be stored securely and will be available only to members of the research team. Data from this study will be retained for 5 years and then disposed of securely.

What happens if the research team finds abnormalities?

Any clinical concerns raised by this research component will be fed back to the clinician responsible for your relative/family members' health care to act accordingly.

What will happen if I don't want to continue with the study?

After deciding to participate, you can withdraw at any time. You do not need to give us any reason. Withdrawing from the study will not affect your relative/family member 's clinical care in any way. We will retain and continue to use any information you have contributed to the research up to when you decided to withdraw, unless you request that we don't use it.

What happens after the study ends?

The results of the study will be published in scientific journals and might be presented at national or international conferences. The data collected from you will be anonymised (it will not be possible to identify you by these data) and safely stored at South London and Maudsley. All data will be destroyed after 5 years.

How will we use information about you?

We will need to use information from the questionnaires you completed by yourself for this research project. Your answers on those questionnaires will be anonymised and stored on a fully secure online database via an encrypted connection. Data will also be archived at SLaM building. To do analysis, all data will be transferred to King's college London anonymised, meaning you will not be identified because your data will have a code number instead. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are my choices about how my information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can I find out more about how my information is used?

- You can find out more about how we use your information
- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by ringing us on [**07490853030**].
- by contacting South London and Maudsley dataprotectionoffice@slam.nhs.uk

Who has reviewed the study?

The West London Research Ethics Committee has reviewed the study for compliance with medical and ethical standards and for scientific value.

Further information and contact details

If you have any questions about the research, your rights as a participant, you would like to report any problem arising from the research, or communicate your decision about withdrawing from the study, please contact our research fellow:

Contact Details for Further information

If you would like to discuss your potential involvement in this research please contact:
Dr Arteen Ahmed on 07490853030

alternatively email: Arteen.ahmed@kcl.ac.uk

Thank you for considering your participation in this Study.

Appendix 6 – Patient & Carer Consent Forms – CRISP Study

Clinical Response of Impulsivity after Brain Stimulation in Parkinson's disease

Which factors are important in predicting changes in Impulse Control Behaviours (ICBs) following Deep Brain Stimulation (DBS) for Parkinson's disease?

South London and Maudsley NHS Foundation Trust
Institute of Psychiatry, Psychology & Neuroscience (IoPPN)
De Crespigny Park
London SE5 8AF

Principal Investigator
Dr David Okai
Consultant Neuropsychiatrist

Consent Form

Participant Identification number:
Please leave this field blank

Please insert your initials/signature in each ☐box if you agree with the statement.

1. I confirm that I have read the Participant Information Sheet V2.0 dated 12/10/2021 for the above study. I have had the opportunity to ask questions, and these have been answered fully ☐

2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time after participation without giving any reason, and without affecting my future medical care. I understand that if I withdraw, the data I have already contributed will be kept for analysis, unless I explicitly request otherwise ☐

3. I agree to provide an email address and my contact phone details for the research team to communicate with me about the study ☐

4. I consent for my NHS clinical records that are relevant for this research (as specified in the informant sheet) to be accessed by authorised members of the research team and utilised for research purposes ☐

5. I understand that study data will be stored in a secure location at SLaM building and treated as strictly confidential in accordance with the General Data Protection Regulation (GDPR) and any legislation enacted in the UK in respect of the protection of personal data

☐

6. I understand that study data might be shared in anonymised format with researchers in King's College London for analysis purposes

☐

7. I consent for my treating clinicians to be informed of my participation, my results, and any incidental findings (as defined in the information sheet)

☐

8. I agree to take part in the above study

☐

Participants entering the study should sign below:

Name of Patient	Date	Signature

Name of person taking consent	Date	Signature

Instructions:

1. *One copy for the participant*
2. *One copy for the researcher*
3. *One copy for the medical notes*

Clinical Response of Impulsivity after Brain Stimulation in Parkinson's disease

Which factors are important in predicting changes in Impulse Control Behaviours (ICBs) following Deep Brain Stimulation (DBS) for Parkinson's disease?

South London and Maudsley NHS Foundation Trust (SLaM)
Institute of Psychiatry, Psychology & Neuroscience (IoPPN)
De Crespigny Park
London SE5 8AF

Principal Investigator
Dr David Okai
Consultant Neuropsychiatrist

Consent Form

Participant Identification number:
Please leave this field blank

Please insert your initial/signature in each ☐ box if you agree with the statement.

1. I confirm that I have read the Participant Information Sheet V2.0 dated 12/10/2021 for the above study. I have had the opportunity to ask questions, and these have been answered fully ☐

2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time after participation without giving any reason. I understand that if I withdraw, the data I have already contributed will be kept for analysis, unless I explicitly request otherwise ☐

3. I agree to provide an email address and my contact phone details for the research team to communicate with me about the study ☐

4. I understand that study data will be stored in a secure location at SLaM building and treated as strictly confidential in accordance with the General Data Protection Regulation (GDPR) and any legislation enacted in the UK in respect of the protection of personal data ☐

5. I understand that study data will be shared in anonymised format with researchers in King's College London for analysis purposes

☐

6. I agree to take part in the above study

☐

Participants entering the study should sign below:

Name of Caregiver	Date	Signature

Name of person taking consent	Date	Signature

Instructions:

1. *One copy for the participant*
2. *One copy for the researcher*

Appendix 7 – Patient Self-Rated Scales – CRISP Study

South London and Maudsley NHS Foundation Trust

Self-Rated Scales
Patient
T0 (Baseline)

Multicentre Observational Study of Impulsive Behaviours following Deep Brain Stimulation in Parkinson's Disease

CRISP STUDY

Table of Contents

Introduction and Instructions

You have kindly decided to participate in CRISP study; therefore, you are now invited to complete a few self-rated scales once before operation (**BASELINE**), and three times **3-** ,**6-** and **12- month** after the operation. This BASELINE Scale schedule contains scales to be completed by you before the DBS surgery. Each part contains one scale. Please, where instruction is provided, read it carefully before answering the questions. We strongly recommend you complete Part A in presence of your caregiver. Once received, you will have about 1 week to complete this document, so to avoid getting exhausted, it is recommended to complete this document with sufficient rest in between.

After completion, you can either scan and email the document to arteen.ahmed@kcl.ac.uk or post it via addressed and pre-paid royal mail envelope provided.

Participant Name (patient):

Date:

Part - A - *QUIP-RS*

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

Instruction for Participants

Please note that Following questions in QUIP-RS scale specifically ask about thoughts of, urges of, difficulty controlling of and/or engaging in given behaviours over ***last 4 weeks***. For example, if you had a thought about gambling over 4 weeks.

Here is more explanation about each behaviour:

B. Sex (making sexual demands on others, promiscuity, prostitution, change in sexual orientation, masturbation, internet or telephone sexual activities, or pornography)

C. Buying (too much of the same thing or things that you don't need or use)

D. Eating (eating larger amounts or different types of food than in the past, more rapidly than normal, at different times (such as overnight eating), until feeling uncomfortably full, or when not hungry)

E. Hobbyism (specific tasks, hobbies or other organized activities, such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)

F. Punding (repeating certain simple motor activities, such as cleaning, tidying, handling, examining, sorting, ordering, collecting, hoarding, or arranging objects, etc.)

G. Medication Use (consistently taking too much of your Parkinson's medications, or increasing on your own, without medical advice, your overall intake of Parkinson's medications)

And here is more clarification about frequencies of each behaviour:

Never (0) = not at all

Rarely (1) = infrequently or 1 day/week

Sometimes (2) = at times or 2-3 days/week

Often (3) = most of the time or 4-5 days/week

Very often (4) = nearly always or 6-7 days/week

Final Note: please, as recommended above complete QUIP-RS in presence of your caregiver and record any disagreement you had with your caregiver next to the behaviour in question.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

1. How much do you think about the following behaviours (such as having trouble keeping thoughts out of your mind or feeling guilty)?

Gambling?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Sex?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Buying?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Eating?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Performing tasks or hobbies?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Repeating simple activities?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Taking your PD medications?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**

2. Do you have urges or desires for the following behaviours that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?

Gambling?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Sex?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Buying?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Eating?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Performing tasks or hobbies?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Repeating simple activities?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Taking your PD medications?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**

3. Do you have difficulty controlling the following behaviours (such as increasing them over time, or having trouble cutting down or stopping them)?

Gambling?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Sex?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Buying?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Eating?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Performing tasks or hobbies?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Repeating simple activities?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Taking your PD medications?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**

4. Do you engage in activities specifically to continue the following behaviours (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

Gambling?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Sex?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Buying?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Eating?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Performing tasks or hobbies?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Repeating simple activities?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**
Taking your PD medications?	☐**Never (0)**	☐**Rarely (1)**	☐**Sometimes (2)**	☐**Often (3)**	☐**very often (4)**

Scoring Sheet (**this part is for the research team, Please leave it blank**)

Gambling? _____ (0-16)

Sex? _____ (016)

Buying? _____ (0-16)

Eating? _____ (0-16)

Performing tasks or hobbies? _____ (0-32)

Repeating simple activities? _____ (0-16)

Taking your PD medications? _____ (0-16)

Part - B - *PHQ-9*

Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use " √" to indicate your answer)	**Not at All**	**Several Days**	**More than half the days**	**Nearly every day**
1.Little interest or pleasure in doing things	☐0	☐1	☐2	☐3
2.Feeling down, Depressed, or hopeless	☐0	☐1	☐2	☐3
3.Trouble falling or staying asleep, or sleeping too much	☐0	☐1	☐2	☐3
4.Feeling tired or having little energy	☐0	☐1	☐2	☐3
5.Poor appetite or overeating	☐0	☐1	☐2	☐3
6.Feeling bad about yourself or that you are a failure or have let yourself or your family	☐0	☐1	☐2	☐3
7.Trouble concentrating on things, such as reading the newspaper or watching television	☐0	☐1	☐2	☐3
8.Moving more speaking so slowly that other people could have noticed. Or the opposite _ being so fidgety or restless that you have been moving around a lot more than usual	☐0	☐1	☐2	☐3
9.Thoughts that you would be better off dead or of hurting yourself	☐0	☐1	☐2	☐3
Add Columns.		+	+	
Total:				

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all
Somewhat difficult
Very difficult
Extremely Difficult

PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

PHQ-9 Patient Depression Questionnaire

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 √s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 √s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 √s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up √ s by column. For every √: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every √ Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal Depression
5-9	Mild Depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

Part - C - *PDQ-39*

Parkinson's Disease Quality of Life Questionnaire (PDQ-39)

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1.	Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2.	Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3.	Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4.	Had problems walking half a mile?	☐	☐	☐	☐	☐
5.	Had problems walking 100 yards?	☐	☐	☐	☐	☐
6.	Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7.	Had difficulty getting around in public?	☐	☐	☐	☐	☐
8.	Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question*** before going onto the next page.

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
9.	Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐
10.	Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11.	Had difficulty washing yourself?	☐	☐	☐	☐	☐
12.	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13.	Had problems doing up buttons or shoe laces?	☐	☐	☐	☐	☐
14.	Had problems writing clearly?	☐	☐	☐	☐	☐
15.	Had difficulty cutting up your food?	☐	☐	☐	☐	☐
16.	Had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17.	Felt depressed?	☐	☐	☐	☐	☐
18.	Felt isolated and lonely?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before going onto the next page.

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
19.	Felt weepy or tearful?	☐	☐	☐	☐	☐
20.	Felt angry or bitter?	☐	☐	☐	☐	☐
21.	Felt anxious?	☐	☐	☐	☐	☐
22.	Felt worried about your future?	☐	☐	☐	☐	☐
23.	Felt you had to conceal your Parkinson's from people?	☐	☐	☐	☐	☐
24.	Avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25.	Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26.	Felt worried by other people's reaction to you?	☐	☐	☐	☐	☐
27.	Had problems with your close personal relationships?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before going onto the next page.

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
28.	Lacked support in the ways you need from your spouse or partner? *If you do not have a spouse or partner, please tick here* ☐	☐	☐	☐	☐	☐
29.	Lacked support in the ways you need from your family or close friends?	☐	☐	☐	☐	☐
30.	Unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31.	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
32.	Felt your memory was bad?	☐	☐	☐	☐	☐
33.	Had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34.	Had difficulty with your speech?	☐	☐	☐	☐	☐
35.	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before going onto the next page.

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
36.	Felt ignored by people?	☐	☐	☐	☐	☐
37.	Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38.	Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39.	Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***.

Thank you for completing the questionnaire.

Part - D - *EQ-5D Patients*

Health Questionnaire
EQ-5D Patients

Under each heading, please tick the ONE box that best describes your health **TODAY**.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

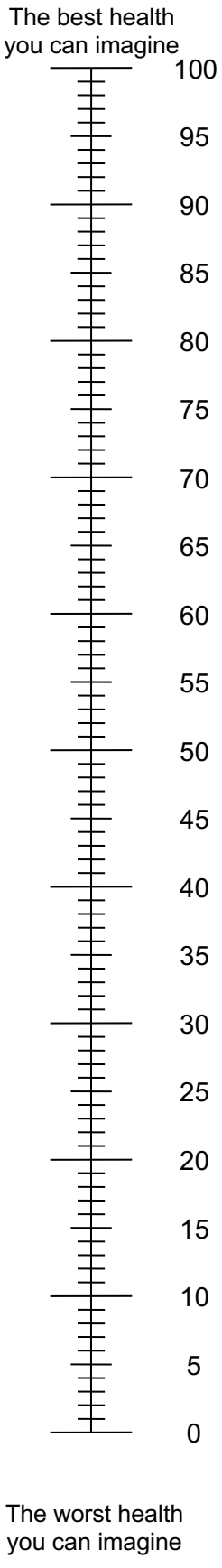
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an **X** on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

_____



Part - E - *WSAS*

Work and Social Adjustment Scale (WSAS)

Instruction
People's problems sometimes affect their ability to do certain day-today tasks in their lives. To rate your problems, look at each section and determine on the scale provided how much your problem impairs your ability to carry out the activity. This assessment is not intended to be a diagnosis. If you are concerned about your results in any way, please speak with a qualified health professional.

If you're retired or choose not to have a job for reasons unrelated to your problem, tick here ☐

0	1	2	3	4	5	6	7	8
Not At all		**Slightly**		**Definitely**		**Markedly**		**Very severely**

1 Because of my Parkinson's, my **ability to work** is impaired. '0' means 'not at all impaired' and '8' means very severely impaired to the point I can't work.

2 Because of my Parkinson's, my **home management** (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired.

3 Because of my Parkinson's, my **social leisure activities** (with other people e.g., parties, bars, clubs, outings, visits, dating, home entertaining) are impaired.

4 Because of my Parkinson's, my **private leisure activities** (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired.

5 Because of my Parkinson's, my ability to form and maintain **close relationships** with others, including those I live with, is impaired.

Total WSAS score =

Part - F - AES

Apathy Evaluation Scale (Self-rated)

For each statement, circle the answer that best describes the subject's thoughts, feelings, and activity in the past 4 weeks.

1. I am interested in things.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

2. I get things done during the day.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

3. Getting things started on my own is important to me.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

4. I am interested in having new experiences.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

5. I am interested in learning new things

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

6. I put little effort into anything.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

7. I approach life with intensity.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

8. Seeing a job through to the end is important to me.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

9. I spend time doing things that interest me.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

10. Someone has to tell me what to do each day.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

11. I am less concerned about my problems than I should be.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

12. I have friends.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

13. Getting together with friends is important to me.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

14. When something good happens, I get excited.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

15. I have an accurate understanding of my problems.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

16. Getting things done during the day is important to me.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

17. I have initiative.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

18. I have motivation.

☐NOT AT ALL ☐SLIGHTLY ☐ SOMEWHAT ☐ A LOT

Part - G - SHAPS

Snaith – Hamilton Pleasure Scale

This questionnaire is designed to measure your ability to experiencepleasurein the last few days. It is important to read each statement very carefully. **Tick one of the boxes [ ] to indicate how much you agree or disagree with each statemen**

1. I would enjoy my favourite television or radio programme:

   Strongly disagree ☐
   Disagree ☐
   Agree ☐
   Strongly agree ☐

2. I would enjoy being with my family or close friends:

   Strongly disagree ☐
   Disagree ☐
   Agree ☐
   Strongly agree ☐

3. I would find pleasure in my hobbies and pastimes:

   Strongly disagree ☐
   Disagree ☐
   Agree ☐
   Strongly agree ☐

4. I would be able to enjoy my favourite meal:

   Strongly disagree ☐
   Disagree ☐
   Agree ☐
   Strongly agree ☐

5. I would enjoy a warm bath or refreshing shower:

   Strongly disagree ☐
   Disagree ☐
   Agree ☐
   Strongly agree ☐

6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

7. I would enjoy seeing other people's smiling faces:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

8. I would enjoy looking smart when I have made an effort with my appearance:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

9. I would enjoy reading a book, magazine or newspaper:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

10. 1 would enjoy a cup of tea or coffee or my favourite drink:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

11. I would find pleasure in small things, e.g., bright sunny day, a telephone call from a friend:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

12. I would be able to enjoy a beautiful and scape or view:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

13. I would get pleasure from helping others:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

14. I would feel pleasure when receiving praise from others:

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

Part - H - UPDRS – Ib & II

Unified Parkinson's Disease Rating Scale

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part Ib: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	
1.7 SLEEP PROBLEMS Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning. 0: Normal: No problems. 1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep. 2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep. 3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night. 4: Severe: I usually do not sleep for most of the night.	*Write or type your response!*
1.8 DAYTIME SLEEPINESS Over the past week, have you had trouble staying awake during the daytime? 0: Normal: No daytime sleepiness. 1: Slight: Daytime sleepiness occurs, but I can resist, and I stay awake. 2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV. 3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people. 4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.	

1.9 PAIN AND OTHER SENSATIONS

Over the past week, have you had uncomfortable feelings in your body like pain, aches, tingling, or cramps?

0: Normal:	No uncomfortable feelings.
1: Slight:	I have these feelings. However, I can do things and be with other people without difficulty.
2: Mild:	These feelings cause some problems when I do things or am with other people.
3: Moderate:	These feelings cause a lot of problems, but they do not stop me from doing things or being with other people.
4: Severe:	These feelings stop me from doing things or being with other people.

1.10 URINARY PROBLEMS

Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents?

0: Normal:	No urine control problems.
1: Slight:	I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities.
2: Mild:	Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents.
3: Moderate:	Urine problems cause a lot of difficulties with my daily activities, including urine accidents.
4: Severe:	I cannot control my urine and use a protective garment or have a bladder tube.

1.11 CONSTIPATION PROBLEMS

Over the past week have you had constipation troubles that cause you difficulty moving your bowels?

0: Normal:	No constipation.
1: Slight:	I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable.
2: Mild:	Constipation causes me to have some troubles doing things or being comfortable.
3: Moderate:	Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything.
4: Severe:	I usually need physical help from someone else to empty my bowels.

1.12 LIGHT HEADEDNESS ON STANDING

Over the past week, have you felt faint, dizzy, or foggy when you stand up after sitting or lying down?

0: Normal:	No dizzy or foggy feelings.
1: Slight:	Dizzy or foggy feelings occur. However, they do not cause me troubles doing things.
2: Mild:	Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down.
3: Moderate:	Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling.
4: Severe:	Dizzy or foggy feelings cause me to fall or faint.

1.13 FATIGUE

Over the past week, have you usually felt fatigued? This feeling is not part of being sleepy or sad.

0: Normal:	No fatigue.
1: Slight:	Fatigue occurs. However, it does not cause me troubles doing things or being with people.
2: Mild:	Fatigue causes me some troubles doing things or being with people.
3: Moderate:	Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything.
4: Severe:	Fatigue stops me from doing things or being with people.

Part II: Motor Aspects of Experiences of Daily Living (M-EDL)

2.1 SPEECH

Over the past week, have you had problems with your speech?

0: Normal:	Not at all (no problems).
1: Slight:	My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself.
2: Mild:	My speech causes people to ask me to occasionally repeat myself, but not every day.
3: Moderate:	My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood.
4: Severe:	Most or all of my speech cannot be understood.

2.2 SALIVA AND DROOLING

Over the past week, have you usually had too much saliva during when you are awake or when you sleep?

0: Normal:	Not at all (no problems).
1: Slight:	I have too much saliva, but do not drool.
2: Mild:	I have some drooling during sleep, but none when I am awake.
3: Moderate:	I have some drooling when I am awake, but I usually do not need tissues or a handkerchief.
4: Severe:	I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.

2.3 CHEWING AND SWALLOWING

Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped, or blended to avoid choking?

0: Normal:	No problems.
1: Slight:	I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared.
2: Mild:	I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week.
3: Moderate	I choked at least once in the past week.
4: Severe:	Because of chewing and swallowing problems, I need a feeding tube.

2.4 EATING TASKS

Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knives, spoons, chopsticks?

0: Normal:	Not at all (no problems).
1: Slight:	I am slow, but I do not need any help handling my food and have not had food spills while eating.
2: Mild:	I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat.
3: Moderate:	I need help with many eating tasks but can manage some alone.
4: Severe:	I need help for most or all eating tasks.

2.5 DRESSING

Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry?

0: Normal:	Not at all (no problems).
1: Slight:	I am slow, but I do not need help.
2: Mild:	I am slow and need help for a few dressing tasks (buttons, bracelets).
3: Moderate:	I need help for many dressing tasks.
4: Severe:	I need help for most or all dressing tasks.

2.6 HYGIENE

Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair, or with other personal hygiene?

0: Normal:	Not at all (no problems).
1: Slight:	I am slow, but I do not need any help.
2: Mild:	I need someone else to help me with some hygiene tasks.
3: Moderate:	I need help for many hygiene tasks.
4: Severe:	I need help for most or all of my hygiene tasks.

2.7 HANDWRITING

Over the past week, have people usually had trouble reading your handwriting?

0: Normal:	Not at all (no problems).
1: Slight:	My writing is slow, clumsy or uneven, but all words are clear.
2: Mild:	Some words are unclear and difficult to read.
3: Moderate:	Many words are unclear and difficult to read.
4: Severe:	Most or all words cannot be read.

2.8 DOING HOBBIES AND OTHER ACTIVITIES

Over the past week, have you usually had trouble doing your hobbies or other things that you like to do?

0: Normal:	Not at all (no problems).
1: Slight:	I am a bit slow but do these activities easily.
2: Mild:	I have some difficulty doing these activities.
3: Moderate:	I have major problems doing these activities, but still do most.
4: Severe:	I am unable to do most or all of these activities.

2.9 TURNING IN BED

Over the past week, do you usually have trouble turning over in bed?

0: Normal:	Not at all (no problems).
1: Slight:	I have a bit of trouble turning, but I do not need any help.
2: Mild	I have a lot of trouble turning and need occasional help from someone else.
3: Moderate:	To turn over I often need help from someone else.
4: Severe:	I am unable to turn over without help from someone else.

2.10 TREMOR

Over the past week, have you usually had shaking or tremor?

0: Normal:	Not at all. I have no shaking or tremor.
1: Slight:	Shaking or tremor occurs but does not cause problems with any activities.
2: Mild:	Shaking or tremor causes problems with only a few activities.
3: Moderate:	Shaking or tremor causes problems with many of my daily activities.
4: Severe:	Shaking or tremor causes problems with most or all activities.

2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR

Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair?

0: Normal:	Not at all (no problems).
1: Slight:	I am slow or awkward, but I usually can do it on my first try.
2: Mild:	I need more than one try to get up or need occasional help.
3: Moderate:	I sometimes need help to get up, but most times I can still do it on my own.
4: Severe:	I need help most or all of the time.

2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another person to walk safely without falling.	
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor? 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze, but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze, I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	
This completes the questionnaire. We may have asked about problems you do not even have and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.	

Part - I – *UPDRS-P*

Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale

Below are a number of statements that describe ways in which people act and think. For each statement, please indicate how much you agree or disagree with the statement. If you **Agree Strongly** circle **1**, if you **Agree Somewhat** circle **2**, if you **Disagree somewhat** circle **3**, and if you **Disagree Strongly** circle **4**. Be sure to indicate your agreement or disagreement for every statement below. Also, there are questions on the following pages.

		Agree Strongly	Agree Some	Disagree Some	Disagree Strongly
1	I have a reserved and cautious attitude toward life.	☐1	☐2	☐3	☐4
2	I have trouble controlling my impulses	☐1	☐2	☐3	☐4
3	I generally seek new and exciting experiences and sensations.	☐1	☐2	☐3	☐4
4	I generally like to see things through to the end.	☐1	☐2	☐3	☐4
5	When I am very happy, I can't seem to stop myself from doing things that can have bad consequences.	☐1	☐2	☐3	☐4
6	My thinking is usually careful and purposeful	☐1	☐2	☐3	☐4
7	I have trouble resisting my cravings (for food, cigarettes, etc.).	☐1	☐2	☐3	☐4
8	I'll try anything once.	☐1	☐2	☐3	☐4
9	I tend to give up easily.	☐1	☐2	☐3	☐4
10	When I am in great mood, I tend to get into situations that could cause me problems	☐1	☐2	☐3	☐4
11	I am not one of those people who blurt out things without thinking.	☐1	☐2	☐3	☐4
12	I often get involved in things I later wish I could get out of.	☐1	☐2	☐3	☐4
13	I like sports and games in which you have to choose your next move very quickly.	☐1	☐2	☐3	☐4
14	Unfinished tasks really bother me.	☐1	☐2	☐3	☐4
15	When I am very happy, I tend to do things that may cause problems in my life	☐1	☐2	☐3	☐4
16	I like to stop and think things over before I do them.	☐1	☐2	☐3	☐4
17	When I feel bad, I will often do things I later regret in order to make myself feel better now.	☐1	☐2	☐3	☐4
18	I would enjoy water skiing.	☐1	☐2	☐3	☐4

Please go to the next page

		Agree Strongly	Agree Some	Disagree Some	Disagree Strongly
19	Once I get going on something I hate to stop.	☐1	☐2	☐3	☐4
20	I tend to lose control when I am in a great mood.	☐1	☐2	☐3	☐4
21	I don't like to start a project until I know exactly how to proceed.	☐1	☐2	☐3	☐4
22	Sometimes when I feel bad, I can't seem to stop what I am doing even though it is making me feel worse.	☐1	☐2	☐3	☐4
23	I quite enjoy taking risks.	☐1	☐2	☐3	☐4
24	I concentrate easily.	☐1	☐2	☐3	☐4
25	When I am really ecstatic, I tend to get out of control.	☐1	☐2	☐3	☐4
26	I would enjoy parachute jumping.	☐1	☐2	☐3	☐4
27	I finish what I start.	☐1	☐2	☐3	☐4
28	I tend to value and follow a rational, "sensible" approach to things.	☐1	☐2	☐3	☐4
29	When I am upset, I often act without thinking.	☐1	☐2	☐3	☐4
30	Others would say I make bad choices when I am extremely happy about something	☐1	☐2	☐3	☐4
31	I welcome new and exciting experiences and sensations, even if they are a little frightening and unconventional.	☐1	☐2	☐3	☐4
32	I am able to pace myself so as to get things done on time.	☐1	☐2	☐3	☐4
33	I usually make up my mind through careful reasoning.	☐1	☐2	☐3	☐4
34	When I feel rejected, I will often say things that I later regret.	☐1	☐2	☐3	☐4
35	Others are shocked or worried about the things I do when I am feeling very excited.	☐1	☐2	☐3	☐4
36	I would like to learn to fly an airplane.	☐1	☐2	☐3	☐4
37	I am a person who always gets the job done.	☐1	☐2	☐3	☐4
38	I am a cautious person.	☐1	☐2	☐3	☐4
39	It is hard for me to resist acting on my feelings.	☐1	☐2	☐3	☐4
40	When I get really happy about something, I tend to do things that can have bad consequences.	☐1	☐2	☐3	☐4
41	I sometimes like doing things that are a bit frightening.	☐1	☐2	☐3	☐4
42	I almost always finish projects that I start.	☐1	☐2	☐3	☐4
43	Before I get into a new situation, I like to find out what to expect from it.	☐1	☐2	☐3	☐4
44	I often make matters worse because I act without thinking when I am upset	☐1	☐2	☐3	☐4
45	When overjoyed, I feel like I can't stop myself from going overboard.	☐1	☐2	☐3	☐4

Please go to the next page

		Agree Strongly	Agree Some	Disagree Some	Disagree Strongly
46	I would enjoy the sensation of skiing very fast down a high mountain slope.	☐1	☐2	☐3	☐4
47	Sometimes there are so many little things to be done that I just ignore them all.	☐1	☐2	☐3	☐4
48	I usually think carefully before doing anything.	☐1	☐2	☐3	☐4
49	When I am really excited, I tend not to think of the consequences of my actions.	☐1	☐2	☐3	☐4
50	In the heat of an argument, I will often say things that I later regret.	☐1	☐2	☐3	☐4
51	I would like to go scuba diving.	☐1	☐2	☐3	☐4
52	I tend to act without thinking when I am really excited.	☐1	☐2	☐3	☐4
53	I always keep my feelings under control.	☐1	☐2	☐3	☐4
54	When I am really happy, I often find myself in situations that I normally wouldn't be comfortable with.	☐1	☐2	☐3	☐4
55	Before making up my mind, I consider all the advantages and disadvantages.	☐1	☐2	☐3	☐4
56	I would enjoy fast driving.	☐1	☐2	☐3	☐4
57	When I am very happy, I feel like it is ok to give in to cravings or overindulge.	☐1	☐2	☐3	☐4
58	Sometimes I do impulsive things that I later regret.	☐1	☐2	☐3	☐4
59	I am surprised at the things I do while in a great mood.	☐1	☐2	☐3	☐4

Thank you for completing questionnaires!

CRISP Research Team

Appendix 8 – Carer Self-Rated Scales – CRISP Study

South London and Maudsley NHS Foundation Trust

Self-Rated Scales
Carer
T0 (Baseline)

Multicentre Observational Study of Impulsive Behaviours following Deep Brain Stimulation in Parkinson's Disease

CRISP STUDY

Received, completed and returned by Email

Introduction and Instructions

You have kindly decided to participate in CRISP study; therefore, you are now invited to complete two self-rated scales once before operation (**BASELINE**), and three times **3-** ,**6-** and **12- month** after the operation. This BASELINE Scale schedule contains two scales to be completed before your patient undergoes DBS surgery. Each part contains one scale. Please, where instruction is provided, read it carefully before answering the questions. Once received, you will have about 1 week to complete this document, so to avoid getting exhausted, it is recommended to complete this document with enough rest in between. If you have any question, please do not hesitate to contact us using below contact details:

Mobile: 07490853030
Email: arteen.ahmed@kcl.ac.uk

After completion, post it via the same addressed and pre-paid royal mail envelope provided with the introductory package.

Participant Name (carer):

Date:

Health Questionnaire

EQ-5D Patients

Under each heading, please tick the ONE box that best describes your health **TODAY**.

The best health you can imagine

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

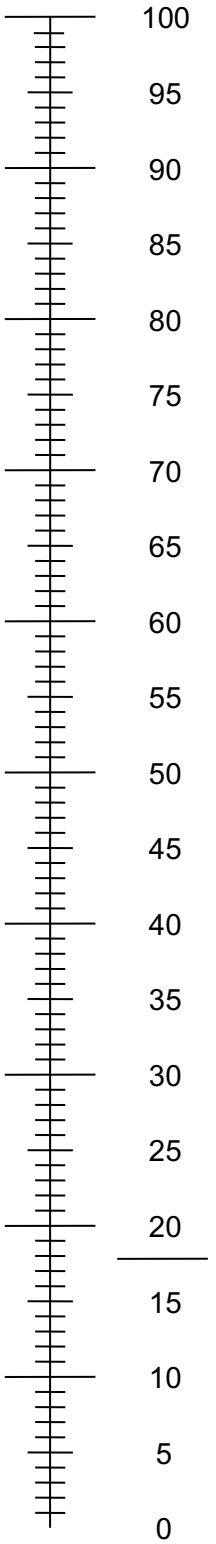
PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an **X** on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.



Part - B - *ZBI Caregivers*

ZARIT BURDEN INTERVIEW ZBI – Caregiver

INSTRUCTIONS: The following is a list of statements, which reflect how people sometimes feel when taking care of another person. After each statement, indicate how often you feel that way: never, rarely, sometimes, quite frequently, or nearly always. There are no right or wrong answers.

	Never	**Rarely**	**Sometimes**	**Quite Frequently**	**Nearly Always**
1) Do you feel that because of the time you spend with your relative you don't have enough time for yourself?	☐0	☐1	☐2	☐3	☐4
2) Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	☐0	☐1	☐2	☐3	☐4
3) Do you feel angry towards your relative when you are around him/her?	☐0	☐1	☐2	☐3	☐4
4) Do you feel that your relative currently affects your relationship with other family members or friends in a negative way?	☐0	☐1	☐2	☐3	☐4
5) Do you feel strained when you are around your relative?	☐0	☐1	☐2	☐3	☐4
6) Do you feel your health has suffered because of your involvement with your relative?	☐0	☐1	☐2	☐3	☐4
7) Do you feel that you don't have as much privacy as you would like because of your relative?	☐0	☐1	☐2	☐3	☐4
8) Do you feel that your social life has suffered because you are caring for your relative?	☐0	☐1	☐2	☐3	☐4
9) Do you feel you have lost control of your life since your relative's illness?	☐0	☐1	☐2	☐3	☐4

10) Do you feel uncertain about what to do about your relative?	☐0	☐1	☐2	☐3	☐4
11) Do you feel you should be doing more for your relative?	☐0	☐1	☐2	☐3	☐4
12) Do you feel you could do a better job in caring for your relative?	☐0	☐1	☐2	☐3	☐4

Appendix 9 – Research Fellow Rated Scales – CRISP Study

South London and Maudsley NHS Foundation Trust

Interview Schedule
Research Fellow rated
T0 (Baseline)

Multicentre Observational Study of Impulsive Behaviours following Deep Brain Stimulation in Parkinson's Disease

CRISP STUDY

Table of Contents

Introduction and Instructions

Scales in this document are designed to be administered by an interviewer. All scales are suitable to be completed over phone. On average the time required to complete each scale tends to vary from 5 minutes to 15 minutes maximum. Part A, the Parkinson's Impulse Control Scale (PICS) is a semi-structured interview designed to investigate presence of an active impulsive behaviour, and further investigate its severity and social impact. It is administered only to participants who have scored above *one* in self-rated QUIP-RS. But the rest of the remaining scales will be administered to all participants. Part E, The *NPI-12* will be administered to an informant, preferably the caregiver. These scales will be administered four times; *baseline*, *3-, 6-, 12- month* after operation by research fellow, Arteen Ahmed.

Participant Name (patient):
Participant ID (patient):

Date:

Part - A - *PICs*

PARKINSON'S IMPULSE CONTROL SCALE PICS- FULL CLINICIAN

Introduction to patient

- I am going to ask you some questions about normal behaviours such as eating and sex or activities such as gambling and shopping.
- In Parkinson's sometimes these behaviours can occur at unusual levels. This can cause concern or problems.
- I am going to ask you a number of questions to see if there have been any such problems over the last month
- Some of the questions may seem quite personal. Please, try to answer each one as honestly and openly as possible.
- If you are unsure about the question or how to answer, just ask.

Section A. EATING

Screening questions

Over the past month, have there been any times when you have eaten an unusually large amounts of food (or certain types of food) even when not hungry? This includes eating larger amounts, different types of food than previously (such as sweeter things), craving food or eating more rapidly than normal. Do you find yourself eating until you are uncomfortably full? (circle)

☐ No [NB Score 0 even if compulsive eating previously but not in the past month]

☐ Yes , If 'Yes' document which from above:

and then continue. If no continue to section B.

Did they have this behaviour before their Parkinson disease? (even if the behaviour was less severe than now)

0 ☐ No

1 ☐ Yes

Do you or your partner believe this behaviour has worsened in relation to Parkinson's disease and associated medications? (circle)

0 ☐ No

1 ☐ Yes

2 ☐ Engaged in eating binges prior to Parkinson's disease but now worse

If 'Yes' (response 1 or 2) continue. If no continue to next section.

Clinician agree given patient/carer account and what is known from history?
0 ☐ No (circle)

1 ☐ Yes
If 'Yes' continue. If no continue to next section.

Intensity of compulsive eating

1. *How often would you say this occurred in an average month? (e.g. over the past 6 months). What is the average number of times you would eat excessively? What would be the most?* [NB: Include all forms of abnormal eating behaviour]

	Average	Max
☐ Less than once a month	1	1☐
☐ Once a month	2	2☐
☐ 1 to 3 times a month	3	3☐
☐ 1 to 3 times a week	4	4☐
☐ 4 to 6 times a week	5	5☐
☐ Once a day	6	6☐
☐ 1 to 3 times a day	7	7☐
☐ More than 3 times a day	8	8☐

2. *How often have you eaten excessively in the past month?* (rate 1-8)
3. *In the past month, how often episodes have you felt like you have lost control of your eating (e.g. eating much more than normal, eating at unusual times for instance during the night or soon after a meal)? What is the average it is likely to be? What is the most?*

	Average	Max
☐ Less than once a month	1	1☐
☐ Once a month	2	2☐
☐ 1 to 3 times a month	3	3☐
☐ 1 to 3 times a week	4	4☐
☐ 4 to 6 times a week	5	5☐
☐ Once a day	6	6☐
☐ 1 to 3 times a day	7	7☐
☐ More than 3 times a day	8	8☐

4. *How <u>long</u> do you spend on these eating episodes on each session in the past month? What is the average time? What is the longest time?*

	Average	Max
☐ Less than 5 minutes	1	1☐
☐ 5-10 minutes	2	2☐
☐ 10-20 minutes	3	3☐
☐ 20-30 minutes	4	4☐
☐ 30-60 minutes	5	5☐
☐ 1-2 hours	6	6☐
☐ 2-4 hours	7	7☐
☐ More than 4 hours	8	8☐

5. *In the <u>past month</u>, how much time do you spend thinking about food per day?*

	Average	Max
☐ Less than 5 minutes	1	1☐
☐ 5-10 minutes	2	2☐
☐ 10-20 minutes	3	3☐
☐ 20-30 minutes	4	4☐
☐ 30-60 minutes	5	5☐
☐ 1-2 hours	6	6☐
☐ 2-4 hours	7	7☐
☐ More than 4 hours	8	8☐

6. *What is the <u>largest</u> amount of food you have eaten in the past month? What did you eat at the time? [describe food stuff and quantity (grams/pounds- estimate kcal)*

Impact of compulsive eating

7. *Has your eating affected your ability to do other things that you would like to do?*

☐ 0 No impact
☐ 1 Slight impact caused by time spent thinking about, acquiring and eating; or caused by cost of food on other activities.
☐ 2 Moderate impact caused by time spent thinking about, acquiring and eating; or caused by cost of food on other activities.
☐ 3 Marked impact caused by time spent thinking about, acquiring and eating; or caused by cost of food on other activities.
☐ 9 NA

8. *In the <u>past 6 months</u> have put on weight due to your eating?*

- ☐0 No weight gain
- ☐1 Has put on 1 to 4 kg weight (2 Ib to 9 Ib)
- ☐2 Has put on 4 to 13kg (10 Ib to 29 Ib)
- ☐3 Has put on >13kg (30Ib)

Actual amount

9. *Are you concerned about your eating? Do you think it is problem? Are you always open about any the amount you eat to friends and family?*

- ☐0 No worry or does not admit to worry. Does not consider it a problem.
- ☐1 Slight worry reported or apparent from interview. Does not consider it a problem
- ☐2 Moderate worry and/or considers eating a problem. May hide action on occasion.
- ☐3 Marked concern. Considers eating a serious problem. Hides/lies about amounts often.

10. *Is your eating a concern for your family or friends? Do they think it is a problem?*

- ☐0 Others do not express any concern. Do not think it is a problem.
- ☐1 Others express slight concern. Do not think it is a real problem
- ☐2 Others express moderate concern and/or consider eating a problem
- ☐3 Others express marked concern. Consider eating a serious problem.

Compulsive eating intensity in past month (* High/Low stake value needs to take into account individual circumstances)

- ☐0 No compulsive eating behaviour in past month
- ☐1 Infrequent small amount of food in addition to normal diet. No Large binges*.
- ☐2 More frequent eating of small amounts especially sweet or high caloric foods and/or occasional large amounts.
- ☐3 Very frequent snacking on sweet or high calorie food. Abnormal eating pattern and/or frequent binges.
- ☐4 Very frequent large binges. Abnormal eating pattern (significant health implications.

Compulsive eating impact in past month

- ☐0 No compulsive eating behaviour in past month
- ☐1 No or minimal impact on other activities. No worry or concern expressed by self or others. Self-limited eating behaviours.
- ☐2 Moderate impact on psychosocial areas. Some concern expressed by self and/or others. Not fully open about eating activities.
- ☐3 Significant psychosocial impact. Has stolen or used deception to continue eating. Hides activities. Marked concern expressed by self and/or others.

Compulsive eating Intensity x Impact Score

Interviewer confidence in ratings

1 ☐Low confidence in accuracy of ratings. Likely to underestimate scale of true problem.
2 ☐Acceptable confidence in accuracy of ratings. Probably reflects approximate nature ☐and scale of problem.
3 ☐Good confidence in accuracy of ratings. Likely to reflect true nature and scale of problem.

Section B. Gambling

Screening questions

Over the past month have you gambled or placed a bet? This includes any form of gambling - scratch cards, National Lottery, bingo, slot machines, card games, betting on horse races or football matches. (circle)

0 ☐No [NB Score 0 even if gambled previously but not in the past month]

1 ☐Yes

If 'Yes' document which from above:_____
and then continue. If no continue to section C.

Did they have this behaviour before their Parkinson disease? (even if the behaviour was less severe than now)

0 ☐No

1 ☐Yes

Do you or your partner believe this behaviour has worsened in relation to Parkinson's disease and associated medications? (circle)

0 ☐No

1 ☐Yes

2 ☐Engaged in gambling behaviour prior to Parkinson's disease but now worse

If 'Yes' (response 1 or 2) continue. If no continue to section C

Clinician agree given patient/carer account and what is known from history?

0 ☐No (circle)

1 ☐Yes

If 'Yes' continue. If no continue to section C.

1. How often would you gamble in an average month? (e.g. over the past 6 months). What is the average number of times you would gamble? What would be the most? [NB: Include all forms of gambling behaviour]

	Average	Max
☐ Less than once a month	1	1☐
☐ Once a month	2	2☐
☐ 1 to 3 times a month	3	3☐
☐ 1 to 3 times a week	4	4☐
☐ 4 to 6 times a week	5	5☐
☐ Once a day	6	6☐
☐ 1 to 3 times a day	7	7☐
☐ More than 3 times a day	8	8☐

2. How often have you gambled in the past month? (rate 1-8)
3. How <u>long</u> do you spend gambling on each session in the past month? What is the average? What is the longest?

	Average	Max
☐ Less than 5 minutes	1	1☐
☐ 5-10 minutes	2	2☐
☐ 10-20 minutes	3	3☐
☐ 20-30 minutes	4	4☐
☐ 30-60 minutes	5	5☐
☐ 1-2 hours	6	6☐
☐ 2-4 hours	7	7☐
☐ More than 4 hours	8	8☐

4. In the past month, what is the typical size of your bet? What is the average? What is the largest?

	Average	Max
☐ ≤10p	1	1☐
☐ 10p-19p	2	2☐
☐ 20p-49p	3	3☐
☐ 50p-99p	4	4☐
☐ £1-£4.99	5	5☐
☐ £5-£9.99	6	6☐
☐ £10-£20	7	7☐
☐ >£20	8	8☐

5. In the past month, how many bets of these sizes would you place in a typical session?

	Average	Max
☐1	1	1☐
☐2-3	2	2☐
☐4-5	3	3☐
☐5-10	4	4☐
☐11-15	5	5☐
☐16-25	6	6☐
☐26-50	7	7☐
☐>50	8	8☐

6. What is the largest single bet you have placed in the past month?

£

7. In the past month, what is the largest amount that you have won in a single session?

[NB session of gambling, not single bet]

£

8. In the past month, what is the largest amount that you have lost in a single session? £

Impact of gambling

9. When you have lost money in the past month, has it affected your ability to do other things that you would like to do, or to pay for essential items? Have you had to cut back your spending on treats? Have you had problems paying for bills or having enough money for food or other essentials?

☐0 No impact
☐1 Slight impact on other discretionary activities
☐2 Moderate impact on discretionary activities and/or some impact on non-discretionary expenditure.
☐3 Marked impact on other discretionary activities and/or definite impact on non-discretionary expenditure

10. In the past month have you borrowed money from a family member or friend in order to gamble? How often? Do they know what the money is for? Have you ever taken money from them without telling, intending to replace it afterwards?

☐0 Has not borrowed/taken money
☐1 Has borrowed occasionally (1-2 times)
☐2 Borrows money regularly (>2 times in past month) with their knowledge.
☐3 Has taken money from another person without asking permission, and/or borrows with deception

11. Are you concerned about your gambling? Do you think it is problem? Are you always open about any losses?

☐0 No worry or does not admit to worry. Does not consider it a problem.
☐1 Slight worry reported or apparent from interview. Does not consider it a problem No debt.
☐2 Moderate worry and/or considers gambling a problem. May be some debt. May hide some losses.
☐3 Marked concern. Considers gambling a serious problem. Significant debt. Hides/lies about losses.

12. Is your gambling a concern for your family or friends? Do they think it is a problem?

☐0 Others do not express any concern. Do not think it is a problem.
☐1 Others express slight concern. Do not think it is a real problem
☐2 Others express moderate concern and/or consider gambling a problem
☐3 Others express marked concern. Consider gambling a serious problem.

Gambling Intensity in past month (* High/Low stake value needs to take into account individual circumstances)
☐1 Infrequent low stake* betting. No High stake* betting. Minimal loss risk.
☐2 More frequent low stake betting, and/or occasional high stake betting. Moderate loss risk.
☐3 Very frequent low stake betting and/or frequent high stake betting. High loss risk.
☐4 Very frequent high stake betting. Very high loss risk.

Gambling Impact in past month
☐1 No or minimal impact on other activities, or non-discretionary expenditure. No worry or concern expressed by self or others. Gambling within financial means. No debt. No borrowing.
☐2 Moderate social/financial impact on other areas of expenditure. Some/occasional debt. Has borrowed to fund gambling. Some concern expressed by self and/or others. Not fully open about loses.
☐3 Significant social/financial impact. Significant debt problem. Has stolen or used deception to fund gambling. Hides losses. Marked concern expressed by self and/or others.

Gambling Intensity x Impact Score [NB Score 0, if no gambling behaviour]

Interviewer confidence in ratings
☐1. Low confidence in accuracy of ratings. Likely to underestimate scale of true problem.
☐2. Acceptable confidence in accuracy of ratings. Probably reflects approximate nature and scale of problem.
☐3. Good confidence in accuracy of ratings. Likely to reflect true nature and scale of problem.

Section C. Compulsive Sexual activity

Screening questions
Over the past month, have you engaged in any sexual activity? Had thoughts about sex? Have you asked for sex from another person? Had an orgasm? (This includes masturbation, making sexual demands on others, promiscuity, prostitution, internet or telephone sexual activities, or pornography) (circle)

0 ☐No [NB Score 0 even if sexual activity previously but not in past month]

1 ☐Yes

If 'Yes' document which from above_____and continue. **If no continue to section D.**

Did they have this behaviour before their Parkinson disease? (even if the behaviour was less severe than now)

0 ☐No

1 ☐Yes

Do you or your partner believe this behaviour has worsened in relation to Parkinson's disease and associated medications? (circle)

0 ☐No

1 ☐Yes

2 Engaged in sexual activity prior to Parkinson's disease but now worse

If 'Yes' (response 1 or 2) continue. If no continue to section D.

Clinician agree given patient/carer account and what is known from history?

0 ☐No (circle)

1 ☐Yes

If 'Yes' continue. If no continue to section D.

Intensity of sexual activity

1. *How <u>often</u> would you engage in any of these activities in an average month? (e.g. over the past 6 months). What is the average number of times you would ? What would be the most?* [NB: Include all forms of sexual behaviour]

	Average	Max
☐ Less than once a month	1	1☐
☐ Once a month	2	2☐
☐ 1 to 3 times a month	3	3☐
☐ 1 to 3 times a week	4	4☐
☐ 4 to 6 times a week	5	5☐
☐ Once a day	6	6☐
☐ 1 to 3 times a day	7	7☐
☐ More than 3 times a day	8	8☐

2. *How often have you engaged in these types of behaviour in the <u>past month?</u>* (rate 1-8)

3. *How <u>long</u> do you spend in each session doing in the past month? What is the average? What is the longest? NB: If a range of sexual activities focus on the most significant*

	Average	Max
☐ Less than 5 minutes	1	1☐
☐ 5-10 minutes	2	2☐
☐ 10-20 minutes	3	3☐
☐ 20-30 minutes	4	4☐
☐ 30-60 minutes	5	5☐
☐ 1-2 hours	6	6☐
☐ 2-4 hours	7	7☐
☐ More than 4 hours	8	8☐

4. In the <u>past month</u>, how long do you spend looking at pornography or other forms of sexual material? What is the average? What is the longest?

	Average	Max
☐ Less than 5 minutes	1	1☐
☐ 5-10 minutes	2	2☐
☐ 10-20 minutes	3	3☐
☐ 20-30 minutes	4	4☐
☐ 30-60 minutes	5	5☐
☐ 1-2 hours	6	6☐
☐ 2-4 hours	7	7☐
☐ More than 4 hours	8	8☐

5. *In the <u>past month</u>, how much of your day do you spend thinking about sex or seeking sexual experiences (including imagery, time spent fantasising about an ongoing or wished for sexual relationship).*

	Average	Max
☐ Less than 5 minutes	1	1☐
☐ 5-10 minutes	2	2☐
☐ 10-20 minutes	3	3☐
☐ 20-30 minutes	4	4☐
☐ 30-60 minutes	5	5☐
☐ 1-2 hours	6	6☐
☐ 2-4 hours	7	7☐
☐ More than 4 hours	8	8☐

6. *What is the <u>longest time</u> you spent on a continuous period of sexual activity in the <u>past month?</u>*

7. *In the <u>past month</u>, what is the longest amount of time engaged in sexual related activity in a single day?* [NB single day, not single session]

8. *Have there been any days when you have not engaged in any sexually related activity*
Y/N

Impact of sexual activity

9. *Over the <u>past month</u>, has involvement in these activities affected your ability to do other things that you would like to do? Do you or your partner feel it has affected their ability for reciprocal affection?*

☐ 0 No impact
☐ 1 Slight impact on other day to day activities.
☐ 2 Moderate impact on other day to day activities and/or some impact on relationship
☐ 3 Marked impact on other day to day activities and/or definite impact on relationship
☐ 9 NA [Not in a relationship]

10. *Have you hidden these behaviours from others? Does your partner know you engage in these activities and how often they occur? Has there been any financial cost? Has this behaviour got you into trouble with the law? Do you think it has affected how other people act to you? Have you placed yourself at risk of acquiring a sexually transmitted disease since your increase or change in sexual activity?*

☐ 0 No financial, social, legal or health costs
☐ 1 Low financial or social costs and manageable. No other consequences
☐ 2 Noticeable financial and social costs.
☐ 3 Significant costs involving social or legal sanction or health risk

11. Are you concerned about your sexual behaviour(s)? Do you think it is problem? Are you always open it to your partner?

☐0 No worry or does not admit to worry. Does not consider it a problem.
☐1 Slight worry reported or apparent from interview. Does not consider it a problem. Open about activity to partner.
☐2 Moderate worry and/or considers sexual behaviour a problem. May hide some activities.
☐3 Marked concern. Considers sexual behaviour a serious problem. Hides/lies about the activity.

12. Is your sexual behaviour a concern for your family or friends? Do they think it is a problem?

☐0 Others do not express any concern. Do not think it is a problem.
☐1 Others express slight concern. Do not think it is a real problem
☐2 Others express moderate concern and/or consider sexual activity a problem (e.g. excessive sexual demands).
☐3 Others express marked concern. Consider sexual activity a serious problem.

Intensity of sexually related activity in past month (* A non-paraphilic (normative) /Paraphilic (non-normative) including prostitution and promiscuity (needs to take into account individual circumstances).

- ☐1 Infrequent normative activity or symptoms from category A. No Category B activities. Minimal risk.
- ☐2 More frequent normative activity or symptoms from Category A. Moderate risks (social, financial or to health).
- ☐3 Very frequent normative activity or symptoms from category A. High risk.
- ☐4 Symptoms from Category B.
- ☐9 N/A [No sexual behaviour in past month]

Impact of sexually related activity in the past month

- ☐1 No or minimal impact on other activities. No worry or concern expressed by self or others..
- ☐2 Moderate social/financial impact. Some concern expressed by self and/or others. Not fully open about activities. Some effect on relationship.
- ☐3 Significant social/financial impact. Deception relating to sexual activities. Marked concern expressed by self and/or others. Significant effect on relationships and reciprocal affection.
- ☐9 N/A [No sexual behaviour in past month]

Sexual Intensity x Impact Score [NB Score 0, if no sexual behaviour]

Interviewer confidence in ratings

1 ☐Low confidence in accuracy of ratings. Likely to underestimate scale of true problem.
2 ☐Acceptable confidence in accuracy of ratings. Probably reflects approximate nature and scale of problem.
3 ☐Good confidence in accuracy of ratings. Likely to reflect true nature and scale of problem.

Category A
include compulsive masturbation, protracted promiscuity, dependence on pornography, phone sex dependence, dependence on sexual accessories such as drugs and severe sexual desire incompatibility

Category B
exhibitionism, paedophilia, voyeurism, fetishism, transvestic-fetishism, sexual sadism, sexual masochism, and frotteurism.

Section D. Compulsive Shopping

Screening questions

Over the past month have there been any times when you have bought too much of the same thing or things you didn't need or use? This includes shopping or browsing in retail stores, on the internet, garage sales antiquing or other shopping activities? (circle)

0 ☐No [NB Score 0 even if abnormal shopping activity previously but not in the past month]

1 ☐ Yes

If 'Yes' document which from above. _____
and continue. . If no continue to section E.

Did they have this behaviour before their Parkinson disease? (even if the behaviour was less severe than now)

0 ☐No

1 ☐Yes

Do you or your partner believe this behaviour has worsened in relation to Parkinson's disease and associated medications? (circle)

0 ☐No

1 ☐Yes

2 ☐Engaged in shopping behaviour prior to Parkinson's disease but now worse

If 'Yes' (response 1 or 2) continue. If no continue to section E.

Clinician agree given patient/carer account and what is known from history?

0 ☐No (circle)

1 ☐Yes

If 'Yes' continue. If no continue to section E.

Intensity of Shopping

1. *How <u>often</u> did you engage in these behaviours in an average month? (e.g. over the past 6 months). What is the average number of times you would go shopping? What would be the most?* [NB: Include all forms of Shopping behaviour]

	Average	Max
☐ Less than once a month	1	1☐
☐ Once a month	2	2☐
☐ 1 to 3 times a month	3	3☐
☐ 1 to 3 times a week	4	4☐
☐ 4 to 6 times a week	5	5☐
☐ Once a day	6	6☐
☐ 1 to 3 times a day	7	7☐
☐ More than 3 times a day	8	8☐

2. *How often have you shopped in the <u>past month?</u>* (rate 1-8)

3. *How <u>long</u> do you spend shopping on each session in the past month? What is the average? What is the longest?*

	Average	Max
☐ Less than 5 minutes	1	1☐
☐ 5-10 minutes	2	2☐
☐ 10-20 minutes	3	3☐
☐ 20-30 minutes	4	4☐
☐ 30-60 minutes	5	5☐
☐ 1-2 hours	6	6☐
☐ 2-4 hours	7	7☐
☐ More than 4 hours	8	8☐

4. *In the <u>past month</u>, what is the <u>typical</u> cost involved in these activities? What is the smallest amount spent? What is the largest amount spent?*

	Average	Max
☐ ≤10p	1	1☐
☐ 10p-19p	2	2☐
☐ 20p-49p	3	3☐
☐ 50p-99p	4	4☐
☐ £1-£4.99	5	5☐
☐ £5-£9.99	6	6☐
☐ £10-£20	7	7☐
☐ >£20	8	8☐

5. *In the <u>past month</u>, how many items would you buy in a single shopping <u>session</u>?*

	Average size	Max size
☐1	1	1☐
☐2-3	2	2☐
☐4-5	3	3☐
☐5-10	4	4☐
☐11-15	5	5☐
☐16-25	6	6☐
☐26-50	7	7☐
☐>50	8	8☐

6. *What is the <u>largest single amount</u> you have spent on an item in the <u>past month</u>*

£

Impact of Shopping

7. *When you have spent money on shopping in the <u>past month</u>, has it affected you ability to do other things that you would like to do, or to pay for essential items? Have you had to cut back your spending on treats? Have you had problems paying for bills or having enough money for food or other essentials?*

☐0 No impact
☐1 Slight impact on other discretionary activities
☐2 Moderate impact on discretionary activities and/or some impact on non-discretionary expenditure.
☐3 Marked impact on other discretionary activities and/or definite impact on non-discretionary expenditure
☐9 NA [Has not lost money]

8. *In the <u>past month</u> have you borrowed money from a family member or friend in order to go shopping? How often? Do they know what the money is for? Have you ever taken money from them without telling, intending to replace it afterwards?*

☐0 Has not borrowed/taken money
☐1 Has borrowed occasionally (1-2 times)
☐2 Borrows money regularly (>2 times in past month) with their knowledge.
☐3 Has taken money from another person without asking permission, and/or borrows with deception

9. *Are you concerned about your shopping? Do you think it is problem? Are you always open about how much you have spent?*

☐0 No worry or does not admit to worry. Does not consider it a problem.
☐1 Slight worry reported or apparent from interview. Does not consider it a problem. No debt.

☐2 Moderate worry and/or considers Shopping a problem. May be some debt. May hide some losses.

☐3 Marked concern. Considers Shopping a serious problem. Significant debt. Hides/lies about losses.

10. Is your shopping a concern for your family or friends? Do they think it is a problem?

☐0 Others do not express any concern. Do not think it is a problem.

☐1 Others express slight concern. Do not think it is a real problem

☐2 Others express moderate concern and/or consider Shopping a problem

☐3 Others express marked concern. Consider Shopping a serious problem.

Shopping Intensity in past month

(* High/Low cost value needs to take into account individual circumstances)

☐1 Infrequent low cost* shopping. No High cost* shopping. Minimal loss risk.

☐2 More frequent low cost shopping, and/or occasional high cost shopping. Moderate loss risk.

☐3 Very frequent low cost shopping and/or frequent high cost shopping. High loss risk.

☐4 Very frequent high cost shopping. Very high risk of spending a significant amount.

☐9 N/A [No Shopping behaviour in past month]

Shopping Impact in past month

☐1 No or minimal impact on other activities, or non-discretionary expenditure. No worry or concern expressed by self or others. Shopping within financial means. No debt. No borrowing.

☐2 Moderate social/financial impact on other areas of expenditure. Some/occasional debt. Has borrowed to fund Shopping. Some concern expressed by self and/or others. Not fully open about loses.

☐3 Significant social/financial impact. Significant debt problem. Has stolen or used deception to fund Shopping. Hides losses. Marked concern expressed by self and/or others.

☐9 N/A [No Shopping behaviour in past month]

Shopping Intensity x Impact Score [NB Score 0, if no Shopping behaviour]

Interviewer confidence in ratings

1 ☐Low confidence in accuracy of ratings. Likely to underestimate scale of true problem.

2 ☐Acceptable confidence in accuracy of ratings. Probably reflects approximate nature and scale of problem.

3 ☐Good confidence in accuracy of ratings. Likely to reflect true nature and scale of problem.

Section E. Off Period Dysphoria

Screening questions

Ask which is most applicable:

Over the <u>past month</u> have you taken more of your Parkinson's medication, than recommended by your Physician or PD nurse or has it been suggested that this is the case? Have you had regular urges for more medication to help with mood/anxiety or distress?

OR

Have you or your partner noticed that you are less panicky after taking a dose of your medication? (circle)

0 ☐No [NB Score 0 even if done previously but not in past month]

1 ☐Yes

9 ☐NOT relevant or Don't know

Please detail below:

Have you adjusted the dose of your DBS stimulator/ apomorphine pump to higher doses than recommended by your Physician or PD nurse? Or has it been suggested that this is so? (circle)

0 ☐No [NB Score 0 even if done previously but not in past month]

1 ☐Yes

9 ☐NOT relevant or Don't know

If 'Yes' document setting it is supposed to be on R _____ L _____
and Adjusted setting R _____ L_____
If yes continue. If no continue to <u>section F</u>.

Clinician agree given patient/carer account and what is known from history? (circle)
0 ☐No
1 ☐Yes **If 'Yes' continue. If no continue to <u>section F</u>.**

CAN I CHECK/YOU TELL ME THE MEDICATION THAT YOU ARE TAKING AT THE MOMENT?

Afterwards, briefly repeat the drug regime to the patient/carer – ask for confirmation of accuracy)

List of participant's Parkinson's medication (including previously discontinued medications) (each Parkinson's medication requires formulation, dose and interval)

Name of tablet	dosage (in mg)	when commenced/discontinued

Please supply full list of extra Parkinson's tablets he/she is taking (often referred to as 'rescue doses')

Name of tablet	dosage (in mg)	Taken how many times per day? (on average)

Intensity of Dopamine Dysregulation Syndrome (DDS)

Do you tend to take the same amount of medication each day?

0 ☐No (circle) continue to Qn 1.

1 ☐ Yes If 'Yes' continue to Qn 6.

11. How many days on average would you take larger amounts of medication than has been prescribed for you?

	Average	Max
☐Less than once a month	1	1☐
☐Once a month	2	2☐
☐1 to 3 times a month	3	3☐
☐1 to 3 times a week	4	4☐
☐4 to 6 times a week	5	5☐
☐Once a day	6	6☐
☐1 to 3 times a day	7	7☐
☐More than 3 times a day	8	8☐

12. *How often have you taken an extra dose of medication in the past month?* (rate 1-8)

13. *When you do take extra doses of medication, how* many would you take in a typical day? *What is the average? What is the most?*

	Average	Max
☐ One tablet	1	1☐
☐ Two tablets	2	2☐
☐ Three tablets	3	3☐
☐ Four tablets	4	4☐
☐ Five tablets	5	5☐
☐ Six tablets	6	6☐
☐ Seven tablets	7	7☐
☐ Eight or more tablets	8	8☐

(Clinician to calculate Levodopa equivalents)

DRUG	CONVERSION FACTOR	
Immediate release L-dopa	**x 1**	
Controlled release L-dopa	**x 0.75**	
Entacapone (or Stalevo) *multiply total of IR and CR l-dopa (after x0.75 conversion), including that obtained from stalevo, x 0.33, then add this to the total	**LD x 0.33**	
Tolcapone	**LD x 0.5**	
Duodopa	**x 1.11**	
Pramipexole	**x 100**	
Ropinirole	**x 20**	
Rotigotine	**x 30**	
Selegiline (oral)	**x 10**	
Selegiline (sublingual)	**x 80**	
Rasagiline	**x 100**	
Amantadine	**x 1**	
Apomorphine	**x 10**	

14. What is the <u>largest single dose</u> you have taken over the course of a day in the <u>past month?</u>

15. *What is the <u>largest single dose</u> you have taken in a single period over the course of a day in the <u>past month?</u>*

16. *In the <u>past month</u>, what is the longest amount of time in a day you have had an off period (where you have been particularly stiff, slow, shaky or low) as a result of your medication wearing off or not working?*

	Average	Max
☐ Less than 30 minutes	1	1☐
☐ 30 minutes to 1 hour	2	2☐
☐ 1-2 hours	3	3☐
☐ 2-3 hours	4	4☐
☐ 3-4 hours	5	5☐
☐ 4-5 hours	6	6☐
☐ 5-6 hours	7	7☐
☐ More than 6 hours	8	8☐

14. *In the past month what is the longest period of time you have been dyskinetic (where you have writhing, wiggling or jerking movements that you find difficult to control)?*

	Average	Max
☐ Less than 30 minutes	1	1☐
☐ 30 minutes to 1 hour	2	2☐
☐ 1-2 hours	3	3☐
☐ 2-3 hours	4	4☐
☐ 3-4 hours	5	5☐
☐ 4-5 hours	6	6☐
☐ 5-6 hours	7	7☐
☐ More than 6 hours	8	8☐

15. How distressing do you find your off periods on a scale of 0 to 4

☐ Not distressing at all	0
☐ Mildly distressing	1
☐ Moderately distressing	2
☐ Severely distressing	3
☐ Incapacitating	4

16. Do you take tablets to help reduce this distress?

0 ☐ No
1 ☐ Yes

17. How distressing do you find being dyskinetic *(writhing, wiggling or jerking movements)* on a scale of 0 to 4

☐ Not distressing at all	0
☐ Mildly distressing	1
☐ Moderately distressing	2
☐ Severely distressing	3
☐ Incapacitating	4

Questions to carer:

18. Do they appear to <u>enjoy</u> taking more of their medication than needed?

0 ☐ No
1 ☐ Yes

19. Are they usually clearly off in their movement functioning (e.g. more stiff, slow or shaky) when they take these 'rescue' doses?

0 ☐ No
1 ☐ Yes

20. Are they usually low in mood, anxious or distressed when they take these 'rescue' doses?

0 ☐ No
1 ☐ Yes

21. Are they usually apparently normal in their movements (not stiff, slow or shaky) but then appear to worry that this will happen (i.e. anticipate going off)?

0 ☐ No
1 ☐ Yes

22. Do they normally take extra medication as a result of medication wearing off early, not working or just randomly?

☐ 1 Wearing off early
☐ 2 Not working
☐ 3 Randomly

Impact of DDS

23. When you have taken additional doses or with your current level of medication, is your movement affected at all? Are you very dyskinetic (where you find you have wiggling, twitching, jerking or other irregular movements)? Do you find that you are have paranoid beliefs that others do not have (which some call delusions) or that you believe your partner is cheating on you?

- ☐ 0 No impact
- ☐ 1 Slight impact on motor functioning, no impact on mental state.
- ☐ 2 Moderate impact on motor activity and/or some impact on mental state (e.g. presence of ICDs
- ☐ 3 Marked impact on motor functioning and/or definite psychotic experience
- ☐ 9 NA

24. Are you always open about the extra doses taken to your doctor or nurse? Do you tend to take more meds if you know you have to go out to a social occasion? Do you find you are hoarding medication? Have you ever made an excuse in order to acquire more medication? Have you ever acquired extra doses of medication on the internet?

- ☐ 0 No extra doses of meds
- ☐ 1 Infrequent extra doses for specific social situation. No attempts to hoard or procure extra meds
- ☐ 2 More frequent extra dosing, Occasional hoarding of medication for this purpose. No attempts to gain extra medication by deception or from sources outside of normal health care providers.
- ☐ 3 Very frequent extra dosing. Will hoard, or use deception to obtain extra doses of medication or attain from sources outside of patient's routine clinical care.

25. Are you concerned about your extra medication use? Do you think it is problem? Are you always open about taking extra doses?

- ☐ 0 No worry or does not admit to worry. Does not consider it a problem.
- ☐ 1 Slight worry reported or apparent from interview. Does not consider it a problem No attempt to hide medication taking.
- ☐ 2 Moderate worry and/or considers DDS a problem. May hide some losses.
- ☐ 3 Marked concern. Considers DDS a serious problem. Hides/lies about losses.

26. Is your use of extra medication a concern for your family or friends? Do they think it is a problem?

- ☐ 0 Others do not express any concern. Do not think it is a problem.
- ☐ 1 Others express slight concern. Do not think it is a real problem
- ☐ 2 Others express moderate concern and/or consider DDS a problem
- ☐ 3 Others express marked concern. Consider DDS a serious problem.

DDS Intensity in past month (* High/Low dosing needs to take into account individual circumstances)

- ☐1 Infrequent additional dosing, minimal motor consequence, no psychiatric consequences.
- ☐2 More frequent additional dosing, moderate motor consequence, little off-period distress (including depression, anxiety and panic).
- ☐3 Frequent additional dosing/ / Shows signs of anxiety when switching off and/or worries about off state / Distressed when off
- ☐4 Very frequent high additional dosing, / high frequency of reported off period distress throughout much of the day
- ☐9 N/A [No DDS behaviour in past month]

DDS Impact in past month

- ☐1 No or minimal impact on other work or recreational activities, No worry or concern expressed by self or others. Additional medication only under specific circumstance.
- ☐2 Moderate social, motor or psychiatric impact. Evidence of Punding or evidence of cumulative build up of meds (e.g. repetitive non purposeful motor behaviour). Some/occasional hoarding of medication. Some concern expressed by self and/or others. Not fully open about amount of extra medication taken.
- ☐3 Significant social/physical or psychiatric impact. Significant hoarding problem. Has procured medication in a non-sanctioned fashion or used deception to this end. Hides amount of medication taken. Marked concern expressed by self and/or others.
- ☐9 N/A [No DDS behaviour in past month]

DDS Intensity x Impact Score [NB Score 0, if no DDS behaviour]

Interviewer confidence in ratings

1 ☐Low confidence in accuracy of ratings. Likely to underestimate scale of true problem.
2 ☐Acceptable confidence in accuracy of ratings. Probably reflects approximate nature and scale of problem.
3 ☐Good confidence in accuracy of ratings. Likely to reflect true nature and scale of problem.

Section F. Punding

Screening questions

Over the past month have you found yourself repeating certain simple behaviours in a manner that could be considered repetitive or has it been suggested that this is the case? (This includes counting, checking, moving of furniture, cleaning and tidying) (circle)

0 ☐No [NB Score 0 even if done previously but not in past month]

1 ☐Yes

9 ☐NOT relevant or Don't know

If no continue to section G.

If 'Yes' please name their activity or activities here

Did they have this behaviour before their Parkinson disease? (even if the behaviour was less severe than now)

0 ☐No

1 ☐Yes

Do you or your partner believe this behaviour has worsened in relation to Parkinson's disease and associated medications? (circle)

0 ☐No

1 ☐Yes

2 ☐Engaged in repetitive behaviour prior to Parkinson's disease but now worse

If 'Yes' (response 1 or 2) continue. If no continue to section G.

Clinician agree given patient/carer account and what is known from history?

0 ☐No (circle)

1 ☐Yes

If 'Yes' continue. If no continue to section G.

Intensity of Punding

1. *How <u>often</u> would you engage in any of these activities in an average month? (e.g. over the past 6 months). What is the average number of times you would ? What would be the most?* [NB: Include all forms of repetitive behaviour]

	Average	Max
☐ Less than once a month	1	1☐
☐ Once a month	2	2☐
☐ 1 to 3 times a month	3	3☐
☐ 1 to 3 times a week	4	4☐
☐ 4 to 6 times a week	5	5☐
☐ Once a day	6	6☐
☐ 1 to 3 times a day	7	7☐
☐ More than 3 times a day	8	8☐

2. *How often have you engaged in these types of behaviour in the <u>past month?</u> (rate 1-8)*

3. *How <u>long</u> do you spend in each session doing in the past month? What is the average? What is the longest? NB: If a range of repetitive activities focus on the most significant*

	Average	Max
☐ Less than 5 minutes	1	1☐
☐ 5-10 minutes	2	2☐
☐ 10-20 minutes	3	3☐
☐ 20-30 minutes	4	4☐
☐ 30-60 minutes	5	5☐
☐ 1-2 hours	6	6☐
☐ 2-4 hours	7	7☐
☐ More than 4 hours	8	8☐

4. How distressing do you find these behaviours on a scale of 0 to 4

☐ Not distressing at all	0
☐ Mildly distressing	1
☐ Moderately distressing	2
☐ Severely distressing	3
☐ Incapacitating	4

5. How calming do you find these behaviours on a scale of 0 to 4

☐ Not calming at all	0
☐ Mildly calming	1
☐ Moderately calming	2
☐ Very calming	3
☐ Will do activity with express	4
☐ Purpose to of calming down	

6. *What is the longest time you spent on a continuous period of punding in the past month*

7. *In the past month, what is the longest amount of time engaged in punding in a single day?* [NB single day, not single session]

8. *Have there been any days when you have not engaged in any such related behaviour or activity*

Y/N

Impact of Punding

9. *Over the past month, has involvement in these activities affected your ability to do other things that you would like to do? Has it affected your relationships with friends/family*

☐ *0 No impact*
☐ *1 Slight impact on other day to day activities.*
☐ *2 Moderate impact on other day to day activities and/or some impact on relationship*
☐ *3 Marked impact on other day to day activities and/or definite impact on relationship*

10. *Are you concerned about your repetitive behaviours/Hobby(s)? Do you think it is problem? Are you always open about the behaviours to your partner?*

☐ 0 No worry or does not admit to worry. Does not consider it a problem.
☐ 1 Slight worry reported or apparent from interview. Does not consider it a problem. Open about activity to partner.
☐ 2 Moderate worry and/or considers punding/ a problem.
☐ 3 Marked concern. Considers punding/ behaviour a serious problem.

11. *Is your repetitive behaviours/Hobby behaviour a concern for your family or friends? Do they think it is a problem?*

☐ 0 Others do not express any concern. Do not think it is a problem.
☐ 1 Others express slight concern. Do not think it is a real problem
☐ 2 Others express moderate concern and/or consider punding/ a problem.
☐ 3 Others express marked concern. Consider punding/ activity a serious problem.

12. Do your activities make mess around the house or result in the area where you perform these activities becoming increasingly untidy?

0 ☐ No
1 ☐ Yes

Intensity of Punding related activity in past month

- ☐ 0 No repetitive behaviour in past month
- ☐ 1 Infrequent activity
- ☐ 2 More frequent activity. Several hours/day or several days per week
- ☐ 3 Very frequent activity. Many hours/day or on a daily basis
- ☐ 4 Behaviours continuous through most of the day

Impact of punding related activity in the past month

- ☐ 0 No repetitive behaviour in past month
- ☐ 1 No or minimal impact on other activities. No worry or concern expressed by self or others..
- ☐ 2 Moderate social/financial impact. Some concern expressed by self and/or others. Not fully open about activities. Some effect on relationship.
- ☐ 3 Significant social/financial impact. Deception involved. Marked concern expressed by self and/or others. Significant effect on social/occupational function.

Punding/ Intensity x Impact Score

Interviewer confidence in ratings

1 ☐ Low confidence in accuracy of ratings. Likely to underestimate scale of true problem.
2 ☐ Acceptable confidence in accuracy of ratings. Probably reflects approximate nature and scale of problem.
3 ☐ Good confidence in accuracy of ratings. Likely to reflect true nature and scale of problem

Section G. Hobbyism

Screening questions

Ask which is most applicable:

Over the past month have you engaged in any specific activity or hobby or has it been suggested that this is the case? (This includes gardening, computer use (although not for the purposes of buying, gambling or sexual activities), DIY, walking or sports (circle)

0 ☐ No [NB Score 0 even if done previously but not in past month]

1 ☐ Yes

9 ☐ NOT relevant or Don't know

If no continue to PART B.
If 'Yes' please name their activity or activities below:

Did they have this behaviour before their Parkinson disease? (even if the behaviour was less severe than now)

0 ☐ No

1 ☐ Yes

Do you or your partner believe this behaviour has worsened in relation to Parkinson's disease and associated medications? (circle)

0 ☐ No

1 ☐ Yes

2 ☐ Engaged in gambling behaviour prior to Parkinson's disease but now worse

If 'Yes' (response 1 or 2) continue. If no continue to PART B.

Clinician agree given patient/carer account and what is known from history?

0 ☐ No (circle)

1 ☐ Yes

If 'Yes' continue. If no continue to PART B.

Intensity of Hobbyism

13. *How <u>often</u> would you engage in any of these activities in an average month? (e.g. over the past 6 months). What is the average number of times you would ? What would be the most?*
[NB: Include all forms of repetitive behaviour]

	Average	Max
☐Less than once a month	1	1☐
☐Once a month	2	2☐
☐1 to 3 times a month	3	3☐
☐1 to 3 times a week	4	4☐
☐4 to 6 times a week	5	5☐
☐Once a day	6	6☐
☐1 to 3 times a day	7	7☐
☐More than 3 times a day	8	8☐

14. How often have you engaged in these types of behaviour in the <u>past month?</u> (rate 1-8)

15. How <u>long</u> do you spend in each session doing in the past month? What is the average? What is the longest? NB: If a range of repetitive activities focus on the most significant

	Average	Max
☐Less than 5 minutes.	1	1☐
☐5-10 minutes	2	2☐
☐10-20 minutes	3	3☐
☐20-30 minutes	4	4☐
☐30-60 minutes	5	5☐
☐1-2 hours	6	6☐
☐2-4 hours	7	7☐
☐More than 4 hours	8	8☐

16. How distressing do you find these behaviours on a scale of 0 to 4

☐Not distressing at all	0
☐Mildly distressing	1
☐Moderately distressing	2
☐Severely distressing	3
☐Incapacitating	4

17. How calming do you find these behaviours on a scale of 0 to 4

☐Not calming at all	0
☐Mildly calming	1
☐Moderately calming	2

☐Most calming activity known 3

18. *What is the longest time you spent on a continuous period of Hobbyism in the past month*

19. *In the past month, what is the longest amount of time engaged in Hobbyism in a single day?* [NB single day, not single session]

20. Have there been any days when you have not engaged in any such related behaviour or activity Y/N

Impact of Hobbyism

1. Over the past month, has involvement in these activities affected your ability to do other things that you would like to do? Has it affected your relationships with friends/family

☐0 No impact
☐1 Slight impact on other day to day activities.
☐2 Moderate impact on other day to day activities and/or some impact on relationship
☐3 Marked impact on other day to day activities and/or definite impact on relationship
☐9 NA

2. *Are you concerned about your repetitive behaviours/Hobby(s)? Do you think it is problem? Are you always open about the behaviours to your partner?*

☐0 No worry or does not admit to worry. Does not consider it a problem.
☐1 Slight worry reported or apparent from interview. Does not consider it a problem. Open about activity to partner.
☐2 Moderate worry and/or considers hobbyism a problem.
☐3 Marked concern. Considers hobbyism behaviour a serious problem.

3. *Is your repetitive behaviours/Hobby behaviour a concern for your family or friends? Do they think it is a problem?*

☐0 Others do not express any concern. Do not think it is a problem.
☐1 Others express slight concern. Do not think it is a real problem
☐2 Others express moderate concern and/or consider hobbyism a problem.
☐3 Others express marked concern. Consider hobbyism activity a serious problem.

4. Do your activities make mess around the house or result in the area where you perform these activities becoming increasingly untidy?

0 ☐ No
1 ☐ Yes

Intensity of hobbyism related activity in past month

- ☐1 Infrequent activity
- ☐2 More frequent activity. Several hours/day or several days per week
- ☐3 Very frequent activity. Many hours/day or on a daily basis
- ☐4 Behaviours continuous through most of the day
- ☐9 N/A [No repetitive behaviour in past month]

Impact of hobbyism related activity in the past month

- ☐1 No or minimal impact on other activities. No worry or concern expressed by self or others..
- ☐2 Moderate social/financial impact. Some concern expressed by self and/or others. Not fully open about activities. Some effect on relationship.
- ☐3 Significant social/financial impact. Deception involved. Marked concern expressed by self and/or others. Significant effect on social/occupational function.
- ☐9 N/A [No repetitive behaviour in past month]

Hobbyism Intensity x Impact Score [NB Score 0, if no hobbyism behaviour]

Interviewer confidence in ratings

1 ☐Low confidence in accuracy of ratings. Likely to underestimate scale of true problem.
2 ☐Acceptable confidence in accuracy of ratings. Probably reflects approximate nature and scale of problem.
3 ☐Good confidence in accuracy of ratings. Likely to reflect true nature and scale of problem.

Part - B – GAD-7 Anxiety

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	☐0	☐1	☐2	☐3
2. Not being able to stop or control worrying	☐0	☐1	☐2	☐3
3. Worrying too much about different things	☐0	☐1	☐2	☐3
4. Trouble relaxing	☐0	☐1	☐2	☐3
5. Being so restless that it is hard to sit still	☐0	☐1	☐2	☐3
6. Becoming easily annoyed or irritable	☐0	☐1	☐2	☐3
7. Feeling afraid, as if something awful might happen	☐0	☐1	☐2	☐3
Column totals	+	+	+	=
				Total score

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Scoring GAD-7 Anxiety Severity

This is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all," "several days," "more than half the days," and "nearly every day." GAD-7 total score for the seven items ranges from 0 to 21.

0–4: minimal anxiety ☐

5–9: mild anxiety ☐

10–14: moderate anxiety ☐

15–21: severe anxiety ☐

Part - C – *NPI-12*

Neuropsychiatric Inventory (NPI-12)

1- Delusions (Not applicable☐)

Does the patient have beliefs that you know are not true (for example, insisting that people are trying to harm him/her or steal from him/her)? Has he/she said that family members are not who they say they are or that the house is not their home? I'm not asking about mere suspiciousness; I am interested if the patient is convinced that these things are happening to him/her.

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the resident believe that he/she is in danger – that others are planning to hurt him/her? ☐
2. Does the patient believe that others are stealing from him/her? ☐
3. Does the patient believe that his/her spouse is having an affair? ☐
4. Does the patient believe that unwelcome guests are living in his/her house? ☐
5. Does the patient believe that his/her spouse or others are not who they claim to be? ☐
6. Does the patient believe that his/her house is not his/her home? ☐
7. Does the patient believe that family members plan to abandon him/her? ☐
8. Does the patient believe that television or magazine celebrities are actually present in the home? [Does he/she try to talk or interact with them?] ☐
9. Does the patient believe any other unusual things that I haven't asked about?

If the screening question is confirmed, determine the frequency and severity of the delusions.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - delusions present but seem harmless and produce little distress in the patient.
- ☐2. Moderate - delusions are distressing and disruptive.
- ☐3. Marked - delusions are very disruptive and are a major source of behavioural disruption. [If PRN medications are prescribed, their use signals that the delusions are of marked severity.]

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

2- Hallucinations ***(Not applicable☐)***

Does the patient have hallucinations such as seeing false visions or hearing imaginary voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive; rather we are asking if the resident actually has abnormal experiences of sounds or visions.

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the patient describe hearing voices or act as if he/she hears voices? ☐
2. Does the patient talk to people who are not there? ☐
3. Does the patient describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc)? ☐
4. Does the patient report smelling odours not smelled by others? ☐
5. Does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her? ☐
6. Does the patient describe tastes that are without any known cause? ☐
7. Does the patient describe any other unusual sensory experiences?

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - hallucinations are present but harmless and cause little distress for the patient.
- ☐2. Moderate - hallucinations are distressing and are disruptive to the patient.
- ☐3. Marked - hallucinations are very disruptive and are a major source of behavioural disturbance. PRN medications may be required to control them.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

3- Agitation/Aggression (Not applicable)

Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes? ☐
2. Is the patient stubborn, having to have things his/her way? ☐
3. Is the patient uncooperative, resistive to help from others? ☐
4. Does the resident have any other behaviours that make him/her hard to handle? ☐
5. Does the patient shout or curse angrily? ☐
6. Does the patient slam doors, kick furniture, throw things? ☐
7. Does the patient attempt to hurt or hit others? ☐
8. Does the resident have any other aggressive or agitated behaviours?

If the screening question is confirmed, determine the frequency and severity of the agitation.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - agitation is disruptive but can be managed with redirection or reassurance.
- ☐2. Moderate - agitation is disruptive and difficult to redirect or control.
- ☐3. Marked - agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

4- Depression/Dysphoria (Not applicable☐)

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the patient have periods of tearfulness or sobbing that seem to indicate sadness? ☐
2. Does the patient say or act as if he/she is sad or in low spirits? ☐
3. Does the patient put him/herself down or say that he/she feels like a failure? ☐
4. Does the patient say that he/she is a bad person or deserves to be punished? ☐
5. Does the patient seem very discouraged or say that he/she has no future? ☐
6. Does the patient say he/she is a burden to the family or that the family would be better off without him/her? ☐
7. Does the patient express a wish for death or talk about killing him/herself? ☐
8. Does the patient show any other signs of depression or sadness? _____

If the screening question is confirmed, determine the frequency and severity of the depression.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - depression is distressing but usually responds to redirection or reassurance.
- ☐2. Moderate - depression is distressing, depressive symptoms are spontaneously voiced by the patient and difficult to alleviate.
- ☐Marked - depression is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

5- Anxiety (Not applicable☐)

Is the patient very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the patient say that he/she is worried about planned events? _____
2. Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense? _____
3. Does the patient have periods of [or complain of] shortness of breath, gasping, or sighing for no apparent reason other than nervousness? _____
4. Does the patient complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? [Symptoms not explained by ill health] _____
5. Does the patient avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds? ☐
6. Does the patient become nervous and upset when separated from you [or his/her caregiver]? [Does he/she cling to you to keep from being separated?] ☐
7. Does the patient show any other signs of anxiety? _____

If the screening question is confirmed, determine the frequency and severity of the anxiety.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - anxiety is distressing but usually responds to redirection or reassurance.
- ☐2. Moderate - anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate.
- ☐3. Marked - anxiety is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

6- Elation/Euphoria (Not applicable☐)

Does the resident seem too cheerful or too happy for no reason? I don't mean the normal happiness but, for example, laughing at things that others do not find funny? I am asking if the patient has a persistent and abnormally good mood or finds humour where others do not.

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the patient appear to feel too good or to be too happy, different from his/her usual self? ☐
2. Does the patient find humour and laugh at things that others do not find funny? ☐
3. Does the patient seem to have a childish sense of humour with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)? ☐
4. Does the patient tell jokes or make remarks that have little humour for others but seem funny to him/her? ☐
5. Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it? ☐
6. Does the patient "talk big" or claim to have more abilities or wealth than is true? ☐
7. Does the patient show any other signs of feeling too good or being too happy?

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - elation is notable to friends and family but is not disruptive.
- ☐2. Moderate - elation is notably abnormal.
- ☐3. Marked - elation is very pronounced; patient is euphoric and finds nearly everything to be humorous.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

7- Apathy/Indifference (Not applicable☐)

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or does he/she lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the patient seem less spontaneous and less active than usual? ☐
2. Is the patient less likely to initiate a conversation? ☐
3. Is the patient less affectionate or lacking in emotions when compared to his/her usual self? ☐
4. Does the patient contribute less to household chores? ☐
5. Does the patient seem less interested in the activities and plans of others? ☐
6. Has the patient lost interest in friends and family members? ☐
7. Is the patient less enthusiastic about his/her usual interests? ☐
8. Does the patient show any other signs that he/she doesn't care about doing new things? _____

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behaviour; patient responds to suggestions to engage in activities.
- ☐2. Moderate - apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.
- ☐3. Marked - apathy is very evident and usually fails to respond to any encouragement or external events.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

8- Disinhibition (Not applicable☐)

Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the patient act impulsively without appearing to consider the consequences? ☐
2. Does the patient talk to total strangers as if he/she knew them? ☐
3. Does the patient say things to people that are insensitive or hurt their feelings? ☐
4. Does the patient say crude things or make sexual remarks that he/she would not usually have said? ☐
5. Does the patient talk openly about very personal or private matters not usually discussed in public? ☐
6. Does the patient take liberties or touch or hug others in way that is out of character for him/her? ☐
7. Does the patient show any other signs of loss of control of his/her impulses? _____

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - disinhibition is notable but usually responds to redirection and guidance.
- ☐2. Moderate - disinhibition is very evident and difficult to overcome by the caregiver.
- ☐3. Marked - disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

9- Irritability/Lability (Not applicable☐)

Does the patient get easily irritated or disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the resident have a bad temper, flying "off the handle" easily over little things? ☐
2. Does the patient rapidly change moods from one to another, being fine one minute and angry the next? ☐
3. Does the patient have sudden flashes of anger? ☐
4. Is the patient impatient, having trouble coping with delays or waiting for planned activities? ☐
5. Is the patient cranky and irritable? ☐
6. Is the patient argumentative and difficult to get along with? ☐
7. Does the patient show any other signs of irritability? _____

If the screening question is confirmed, determine the frequency and severity of the irritability/lability.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - irritability or lability is notable but usually responds to redirection and reassurance.
- ☐2. Moderate - irritability and lability are very evident and difficult to overcome by the caregiver.
- ☐3. Marked - irritability and lability are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major source of distress.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

10- Aberrant Motor Behaviour (Not applicable☐)

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the patient pace around the house without apparent purpose? ☐
2. Does the patient rummage around opening and unpacking drawers or closets? ☐
3. Does the patient repeatedly put on and take off clothing? ☐
4. Does the resident have repetitive activities or "habits" that he/she performs over and over? ☐
5. Does the patient engage in repetitive activities such as handling buttons, picking, wrapping string, etc? ☐
6. Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot? ☐
7. Does the patient do any other activities over and over? _____

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity:

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - abnormal motor activity is notable but produces little interference with daily routines.
- ☐2. Moderate - abnormal motor activity is very evident; can be overcome by the caregiver.
- ☐3. Marked - abnormal motor activity is very evident, usually fails to respond to any intervention by the caregiver, and is a major source of distress.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

11- Sleep (Not applicable☐)

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?

☐NO (If no, please proceed to next screening question). ☐YES (If yes, please proceed to sub-questions).

1. Does the patient have difficulty falling asleep? ☐
2. Does the patient get up during the night (do not count if the resident gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? ☐
3. Does the patient wander, pace, or get involved in inappropriate activities at night? ☐
4. Does the patient awaken you during the night? ☐
5. Does the patient awaken at night, dress, and plan to go out thinking that it is morning and time to start the day? ☐
6. Does the patient awaken too early in the morning (earlier that was his/her habit)? ☐
7. Does the patient sleep excessively during the day? ☐
8. Does the patient have any other night-time behaviours that bother you that we haven't talked about? _____

If the screening question is confirmed, determine the frequency and severity of the night-time behaviour.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present (every night)

Severity:
- ☐1. Mild - night-time behaviours occur but they are not particularly disruptive.
- ☐2. Moderate - night-time behaviours occur and disturb the patient and the sleep of the caregiver; more than one type of night-time behaviour may be present.
- ☐3. Marked - night-time behaviours occur; several types of night-time behaviour may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- 5. Very severely or extremely

12- Appetite and Eating Changes (Not applicable☐)

Has he/she had any change in appetite, weight, or eating habits (count as N/A if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

☐NO (If no, please proceed to PART D). ☐YES (If yes, please proceed to sub-questions).

1. Has he/she had a loss of appetite? ☐
2. Has he/she had an increase in appetite? ☐
3. Has he/she had a loss of weight? ☐
4. Has the resident gained weight? ☐
5. Has he/she had a change in eating behaviour such as putting too much food in his/her mouth at once? ☐
6. Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food? ☐
7. Has the resident developed eating behaviours such as eating exactly the same types of food each day or eating the food in exactly the same order? ☐
8. Have there been any other changes in appetite or eating that I haven't asked about? _____

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

Frequency:
- ☐1. Occasionally - less than once a week.
- ☐2. Often - about once a week.
- ☐3. Frequently - several times per week but less than every day.
- ☐4. Very often – once or more per day or almost continuously present.

Severity:
- ☐1. Mild - changes in appetite or eating are present but have not led to changes in weight and are not disturbing.
- ☐2. Moderate - changes in appetite or eating are present and cause minor changes in weight.
- ☐3. Marked - obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the patient.

Distress: How emotionally distressing do you find this behaviour?
- ☐0. Not at all
- ☐1. Minimally
- ☐2. Mildly
- ☐3. Moderately
- ☐4. Severely
- ☐5. Very severely or extremely

Part – D – UPDRS Part IA

MDS UPDRS
Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Part IA: Complex behaviours: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviours that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT		**SCORE**
Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver. *Instructions to patient [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.]		
0: Normal: ☐	No cognitive impairment.	
1: Slight: ☐	Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions.	
2: Mild: ☐	Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions.	
3: Moderate: ☐	Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions.	
4: Severe: ☐	Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.	

1.2 HALLUCINATIONS AND PSYCHOSIS	**SCORE**
Instructions to examiner: Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory, and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patient's insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patient [and caregiver]: Over the past week have you seen, heard, smelled, or felt things that were not really there?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: ☐ No hallucinations or psychotic behaviour. 1: Slight: ☐ Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2: Mild: ☐ Formed hallucinations independent of environmental stimuli. No loss of insight. 3: Moderate ☐: Formed hallucinations with loss of insight. 4: Severe: ☐ Patient has delusions or paranoia.	

1.3 DEPRESSED MOOD

Instructions to examiner: Consider low mood, sadness, hopelessness, feelings of emptiness, or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions.

Instructions to patient [and caregiver]: Over the past week have you felt low, sad, hopeless, or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities or to be with people? [If yes, examiner asks patient or caregiver to elaborate and probes for information.

0: Normal: ☐	No depressed mood.
1: Slight: ☐	Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions.
2: Mild: ☐	Depressed mood that is sustained over days, but without interference with normal activities and social interactions.
3: Moderate: ☐	Depressed mood that interferes with, but does not preclude the patient's ability to carry out normal activities and social interactions.
4: Severe: ☐	Depressed mood precludes patient's ability to carry out normal activities and social interactions.

1.4 ANXIOUS MOOD

Instructions to examiner: Determine nervous, tense, worried, or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions.

Instructions to patient [and caregiver]: Over the past week have you felt nervous, worried, or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people? [If yes, examiner asks patient or caregiver to elaborate and probes for information.]

0: Normal: ☐	No anxious feelings.
1: Slight: ☐	Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions.
2: Mild: ☐	Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions.
3: Moderate ☐	Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions.
4: Severe: ☐	Anxious feelings preclude patient's ability to carry out normal activities and social interactions.

1.5 APATHY

Instructions to examiner: Consider level of spontaneous activity, assertiveness, motivation, and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression.

Instructions to patient [and caregiver]: Over the past week, have you felt indifferent to doing activities or being with people? [If yes, examiner asks patient or caregiver to elaborate and probes for information.]

0: Normal: ☐	No apathy.
1: Slight: ☐	Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions.
2: Mild: ☐	Apathy interferes with isolated activities and social interactions.
3: Moderate: ☐	Apathy interferes with most activities and social interactions.
4: Severe: ☐	Passive and withdrawn, complete loss of initiative.

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME	SCORE
Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behaviour). Rate the impact of such abnormal activities/behaviours on the patient's personal life and on his/her family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity). *Instructions to patient [and caregiver]: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop?* [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patient. . 0: Normal: ☐ No problems present. 1: Slight: ☐ Problems are present but usually do not cause any difficulties for the patient or family/caregiver. 2: Mild: ☐ Problems are present and usually cause a few difficulties in the patient's personal and family life. 3: Moderate: ☐ Problems are present and usually cause a lot of difficulties in the patient's personal and family life. 4: Severe: ☐ Problems are present and preclude the patient's ability to carry out normal activities	

Part – E- UPDRS - Part IV: Motor Complications

A. DYSKINESIAS [exclusiveofOFF-statedystonia]

	SCORE
4.1 TIME SPENT WITH DYSKINESIAS Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.	

Instructions to patient [and caregiver]: Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep hrs, you are awake hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching, or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking, and irregular movements. Add up all the time during the waking day when these usually occur. How many hours (use this number for your calculations).

0: Normal: ☐	No dyskinesias.
1:Slight: ☐	≤ 25% of waking day.
2:Mild:☐	26 - 50% of waking day.
3: Moderate: ☐	51 - 75% of waking day.
4: Severe: ☐	> 75% of waking day.

1. Total Hours Awake:
2. Total Hours with Dyskinesia

3. % Dyskinesia = ((2/1)*100):

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0: Normal: ☐ 1: Slight: ☐ 2:Mild:☐ 3:Moderate: ☐ 4: Severe: ☐	No dyskinesias or no impact by dyskinesias on activities or social interactions. Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods. Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods. Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes. Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social	
B. MOTOR FLUCTUATIONS		

4.3 TIME SPENT IN THE OFF STATE

Score

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6.

Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time, or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function? (use this number for your calculations).

0: Normal: ☐

1:Slight: ☐

2:Mild: ☐

3: Moderate: ☐

4: Severe: ☐

No OFF time.
≤ 25% of waking day.
26 - 50% of waking day.
51 - 75% of waking day.
> 75% of waking day.

1. Total Hours Awake:
2.Total Hours OFF:
3. % OFF = ((2/1)*100):

4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS	**Score**
Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?* 0: Normal: ☐ No fluctuations or no impact by fluctuations on performance of activities or social interactions. 1: Slight: ☐ Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state. 2: Mild: ☐ Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state. 3: Moderate ☐ Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods. 4: Severe: ☐ Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	

4.5 COMPLEXITY OF MOTOR FLUCTUATIONS | **Score**

Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake, or other factors. Use the information provided by the patients and caregivers and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time, or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer.

Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"

0: Normal: ☐ No motor fluctuations

1: Slight: ☐ OFF times are predictable all or almost all of the time (> 75%).

2: Mild: ☐ OFF times are predictable most of the time (51-75%).

3: Moderate: ☐ OFF times are predictable some of the time (26-50%).

4: Severe: ☐ OFF episodes are rarely predictable (≤ 25%).

C. "OFF" DYSTONIA

` | **Score**

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0: Normal: ☐	No dystonia OR NO OFF TIME.
1:Slight: ☐	≤ 25% of time in OFF state.
2:Mild: ☐	26-50% of time in OFF state.
3:Moderate: ☐	51-75% of time in OFF state.
4: Severe: ☐	> 75% of time in OFF state.

1. Total Hours OFF:
2. Total OFF Hours with Dystonia:
3. % OFF Dystonia = ((2/1)*100):

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

Patient name or Subject ID	Site ID	(mm-dd-year) Assessment date	Investigator's initials

Part – F – *CLINICAL GLOBAL IMPRESSION*

CLINICAL GLOBAL IMPRESSION (CGI-S AND CGI-I)

SEVERITY OF ILLNESS (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

[1] ☐ Normal, not at all ill

[2] ☐ Borderline mentally ill

[3] ☐ Mildly ill

[4] ☐ Moderately ill

[5] ☐ Markedly ill

[6] ☐ Severely ill

[7] ☐ Among the most extremely ill patients

Appendix 10– Substantial Amendment – CRISP Study

Amendment Tool

v1.6 06 December 2021

For office use

QC: No

Section 1: Project information

Short project title*:	Clinical Response of Impulsivity after DBS in Parkinson's Disease 1.0
IRAS project ID* (or REC reference if no IRAS project ID is available):	285162
Sponsor amendment reference number*:	Substantial Amendment 1 (SA1)
Sponsor amendment date* (enter as DD/MM/YY):	25 April 2022
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	We would like to extend the recruitment window, which is currently not specified in the protocol and IRAS form, but it is variably set in the OID of each participating site. We would like to specify that we will close recruitment at all centres in 1/3/2023. We would also like to change the protocol about recruitment window for each participant. Current protocol allows us to recruit a participant within one month before the operation. We would like to change that from 6 weeks before the operation until the activation (programming) of the stimulation after the operation. Which means we can recruit after operation if the stimulation hasn't been activated. In addition, we would like to add a research part, a retrospective study, which will involve only one participating centre, King's College Hospital. In this project, we will retrospectively review clinical notes of patients who have undergone operation since 2018-2021. Finally, Personality Scale "UPPS-P" was scheduled for baseline and 12-month follow up only. We would like to add it to the 6-month follow up.

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**	No		
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	**Yes**		No	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	Yes	No	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		**No**	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		**No**	
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		**No**	
Did the study involve children OR does the amendment introduce this?:	Yes		**No**	
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**		No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes		**No**	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	**Yes**	No	No	No
Which nations had participating NHS/HSC organisations prior to this amendment?	**Yes**	No	**Yes**	No
Which nations will have participating NHS/HSC organisations after this amendment?	**Yes**	No	**Yes**	No

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1				
Area of change (select)*:	Study Design			
Specific change (select - only available when area of change is selected first)*:	Extension to study duration that will not have any additional resource implications for participating organisations - Please specify in the free text below			
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	We would like to extend the recruitment window, which is currently not specified in the protocol and IRAS form, but it is variably set in the OID of each participating site. We would like to specify that we will close recruitment at all centres in 1/3/2023.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 2				
Area of change (select)*:	Participant Procedures			
Specific change (select - only available when area of change is selected first)*:	Participant procedures - minor change that can be implemented within existing resource at participating organisations - Please specify in the free text below			
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	We would also like to change the protocol about recruitment window for each participant. Current protocol allows us to recruit a participant within one month before the operation. We would like to change that from 6 weeks before the operation until the activation (programming) of the stimulation after the operation. Which means we can recruit after operation if the stimulation hasn’t been activated.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	All		**Some**	
			Remove all changes below	

Change 3				
Area of change (select)*:	Study Design			
Specific change (select - only available when area of change is selected first)*:	New arm - Addition of a study arm or placebo/control group			
Further information (free text - note that this field will adapt to the amount of text entered):	Finally, we would like to add a research part, a retrospective study, which will involve only one participating centre, King’s College Hospital. In this project, we will retrospectively review clinical notes of patients who have undergone operation since 2018-2021. This review will be done by the same research fellow which is working on CRISP STUDY. So no additonal researcher is needed.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	All		**Some**	
			Remove all changes below	

Change 4	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Other minor change to study design that can be implemented within existing resource in place at participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in	Personality Scale "UPPS-P" was scheduled to be done at baseline and at 12-month follow up

place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	only. We would like to add it to the 6-month follow up.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	

Add another change

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name [first name and surname]:*	Christina Armoogum
Email address:*	slam-ioppn.research@kcl.ac.uk

Lock for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Lock for submission

After locking the tool, proceed to submit the amendment online. The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																	
	UK wide:						England and Wales:				Scotland:				Northern Ireland:			
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HMPPS	HRA and HCRW Approval	REC (AWIA)	PBPP	SPS (RAEC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	Category:
Change 1:	N					(Y)				(Y)				(Y)					C
Change 2:	N					(Y)				(Y)				(Y)					C
Change 3:	Y					(Y)				(Y)				N					B
Change 4:	N					(Y)				(Y)				(Y)					C
Overall reviews for the amendment:																			
Full review:	Y					N				N				N					
Notification only:	N					Y				Y				Y					
Overall amendment type:	Substantial																		
Overall Category:	B/C																		

Please note: This amendment should **not** be processed via online submission. Please contact the REC directly to submit this amendment. See the "Submission Guidance" tab for further information.

Appendix 11– Non-Substantial Amendment – CRISP Study

Amendment Tool

v1.6 06 December 2021

For office use

QC: No

Section 1: Project information

Short project title*:	Clinical Response of Impulsivity after DBS in Parkinson's Disease 1.0
IRAS project ID* (or REC reference if no IRAS project ID is available):	285162
Sponsor amendment reference number*:	non-substantial 2
Sponsor amendment date* (enter as DD/MM/YY):	08 February 2023
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	Current recruitment period is 1/3/2023. We would like to extend it to 1/12/2023. The requested new recruitment deadline falls in the study time (9/8/2024).

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	Yes	No	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		**No**	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		**No**	
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		**No**	
Did the study involve children OR does the amendment introduce this?:	Yes		**No**	
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**		No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes		**No**	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	**Yes**	No	No	No
Which nations had participating NHS/HSC organisations prior to this amendment?	**Yes**	No	No	No
Which nations will have participating NHS/HSC organisations after this amendment?	**Yes**	No	No	No
Was this a "single site, self sponsored" study in England or Wales prior to this amendment?	Yes		**No**	

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1

Area of change (select)*:	Participant Procedures			
Specific change (select - only available when area of change is selected first)*:	Participant procedures - minor change that can be implemented within existing resource at participating organisations - Please specify in the free text below			
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	Current recruitment period is 1/3/2023. We would like to extend it to 1/12/2023. The requested new recruitment deadline falls in the study time (9/8/2024).			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Add another change	

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name [first name and surname]:*	Christina Armoogum
Email address:*	slam-ioppn.research@kcl.ac.uk

Lock for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Lock for submission

After locking the tool, proceed to submit the amendment online. The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																	
	UK wide:						England and Wales:				Scotland:				Northern Ireland:			
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HMPPS	HRA and HCRW Approval	REC (AWIA)	PBPP	SPS (RAEC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	Category:
Change 1:						(Y)				(Y)									C
Overall reviews for the amendment:																			
Full review:						N				N									
Notification only:						Y				Y									
Overall amendment type:	Non-substantial, no study-wide review required																		
Overall Category:	C																		

Appendix 12 – REC Letter of Approval – CRISP Study

Health Research Authority

London - West London & GTAC Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0207 1048 007

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

08 October 2021

Dr David Okai
Neuropsychiatry Outpatient Department
Maudsley Hospital
Denmark Hill
London
SE5 8AZ

Dear Dr Okai

Study title:	**Which factors are important in predicting changes in Impulse Control Behaviours (ICBs) following Deep Brain Stimulation (DBS) for Parkinson's disease?**
REC reference:	**21/LO/0580**
Protocol number:	**n/a**
IRAS project ID:	**285162**

Thank you for your response to the Research Ethics Committee's request for further information on the above research and for submitting revised documentation. These have been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

If you have not already included registration details in your IRAS application form, you should notify the REC of the registration details as soon as possible.

Further guidance on registration is available at: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

The favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [patient self-rated scales t0 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [patient self-rated scales t1 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [patient self-rated scales t2 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [patient self-rated scales t3 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [carer self-rated scales t0 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [carer self-rated scales t1 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [carer self-rated scales t2 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [carer self-rated scales t3 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [Research fellow Interview schedule t0 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [Research fellow Interview schedule t1 v 1.0 285162]	1.0	02 August 2021
Interview schedules or topic guides for participants [Research fellow Interview schedule t2 v 1.0 285162.docx]	1.0	02 August 2021
Interview schedules or topic guides for participants [Research fellow Interview schedule t3 v 1.0 285162.docx]	1.0	02 August 2021
IRAS Application Form [IRAS_Form_26072021]		26 July 2021
Letter from sponsor [Sponsor-Letter- 285162]		
Letters of invitation to participant [Instruction Sheet v 1.0 285162]	1.0	25 July 2021
Other [PhD Project Approval Form IoPPN 285162]		24 March 2021
Other [Support letter Orion MedTech 285162]		
Other [REC response sheet]		
Participant consent form [Patient Consent Form V2.0 285162]	V2	22 September 2021
Participant consent form [Carer Consent Form V2.0 285162]	v2	22 September 2021
Participant information sheet (PIS) [Patient Information Sheet V2.0 285162]	v2	22 September 2021
Participant information sheet (PIS) [Carer Information sheet V 2.0 285162]	V2	22 September 2021
Referee's report or other scientific critique report [FAST-R General Feedback]		11 September 2020
Referee's report or other scientific critique report [Peer review 1 v.1 1.6.2020]		01 June 2020
Referee's report or other scientific critique report [Peer review 2 v.1 1.6.2020]		01 June 2020
Referee's report or other scientific critique report [Peer review 3 v.1 1.6.2020]		01 June 2020
Research protocol or project proposal [Protocol v 1.0 285162]		15 March 2020
Summary CV for Chief Investigator (CI) [CV Chief investigator Dr Okai 285162]		01 July 2020
Summary CV for student [CV Research Fellow Arteen Ahmed 285162]		

Summary CV for supervisor (student research) [CV Supervisor Dr Shotbolt 285162]		
Summary CV for supervisor (student research) [Supervisor- Aarsland]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high-quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 285162 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

pp
Professor Catherine Urch
Chair

Email: westlondon.rec@hra.nhs.uk

Enclosure: "After ethical review – guidance for researchers"

Copy to: Mr Dunstan Nicol-Wilson,
South London and Maudsley NHS Foundation Trust

Appendix 13– Protocol – The Single Site Audit

Retrospective evaluation of neuropsychiatric clinical notes before and after STN-DBS in Parkinson's disease

Introduction:

King's College Hospital (KCH) is one of the participating centres in the ongoing multicentre observational study – CRISP study. As a prospective study; CRISP study's main objective is to assess the effect of DBS on ICDs and other psychiatric symptoms in patients with PD. One of the strengths of the CRISP study is the use of a unified set of self-rated scales, and semi-structured interviews, across all participating centres to fulfil the main objective. These observations will add valuable data about this important subject. A retrospective analysis of real-world clinical notes can add one more perspective to the CRISP Study; specifically, a comparison of the traditional neuropsychiatric screening interview with the use of rating scales and semi-structured interview techniques The clinical notes reviewed were collected during routine clinical assessment before and, in some patients, after the DBS operation.

The comparison will allow us to draw conclusions about best clinical practice in pre-operative neuropsychiatric assessment on the DBS pathway. As per current CRISP protocol, we report details of any detected psychiatric symptoms to treating clinicians. We hypothesise that, during the routine clinical assessment used on the DBS pathway prior to the start of the CRISP study, a significant proportion of psychiatric symptoms may be undetected. We therefore propose to review retrospective clinical assessments of patients who were assessed on the DBS pathway and compare the prevalence of psychiatric symptoms to the data collected in a prospective unified screening process (in the CRISP study). This comparison will allow us to test the above hypothesis. We will also examine whether earlier detection of pre-operative psychiatric symptoms leads to better post-operative outcomes. Furthermore, this analysis will demonstrate the importance of having a research database that is shared by all UK DBS centres.

Objectives:

- Retrospective description of demographic data and psychiatric symptoms in the cohort of PD patients undergoing DBS surgery at KCH

- Assessment of severity of documented psychiatric symptoms at each visit including onset and duration of symptoms.
- Assessing objective changes [positive or negative] in psychiatric symptoms recorded by assessors over time
- Comparing effectiveness of treatment plan in retrospective psychiatric records with treatment plan in the prospective data of KCH

Methodology and Statistic

A thorough handheld search of the KCH neurosurgery database will be performed to detect all PD patients who had DBS surgery from Jan 2015 until Dec 2021. We will include those who have at least records of one neuropsychiatric assessment before and one follow-up assessments after the surgery. For eligible subjects, pre- and post-operative clinical notes will be reviewed. These clinical notes are recorded by the same neuropsychiatrist during pre-operational assessment and post operational follow-ups. Demographic data and psychiatric records will be extracted. Recorded psychiatric symptoms will be described and if possible, the severity specified. All extracted data will be anonymised.

Using SPSS software, we will run a descriptive data analysis. For each given psychiatric symptom, a variable will be made to indicate its severity and another to indicate its subjective change over time [negative, positive]. The paired Chi-squared test will be used to analyse changes in recorded severity of psychiatric symptoms [mild, moderate, severe] over time. Additionally, using the same test, the association between demographic data, PD duration and psychiatric symptoms frequency or severity will be examined.

Data handling and management

The KCH DBS database will be screened for eligible cases using a KCH computer. Extracted data for eligible cases will be anonymised before sending it via encrypted connection to a secured computer assigned to CRISP research team at SLaM. A copy of anonymised data will also be saved on personal laptop of the research fellow.
As for archiving, no hard copy will be needed to be archived. A soft copy of data will be saved on CRISP computer at SLaM. As for the indemnity, publication and intellectual

property, this retrospective data will be handled as part of CRISP study and the policies in its current protocol v 1.0 will be applied to this retrospective data.

Appendix 14 – Sponsorship Confirmation from SLaM – CRISP study

Subject: 285162 - Confirmation of SLaM Sponsorship
Date: Wednesday, 14 July 2021 at 10:16:47 British Summer Time
From: Batham, Dale
To: Okai, David
CC: Ahmed, Arteen, Shotbolt, Paul, kcl - slam-ioppn.research, KCL SLaM EDGE Support
Attachments: IRAS submission guidance.docx

Dear Dr Okai,

Study Title: Clinical Response of Impulsivity after DBS in Parkinson's Disease 1.0
IRAS Project ID: 285162
Sponsor: South London and Maudsley NHS Foundation Trust

I am pleased to advise that your IRAS application is now ready for sponsorship and that South London and Maudsley NHS Foundation Trust will be sponsor for your study. Instructions for requesting sponsor signature, and booking your study for NHS REC review and HRA Assessment are below. Please include a copy of this email with your application to the REC and HRA.

Please be aware that you will need final written approval from the REC and HRA, and confirmation from this R&D office before you start your study.

Important: If the REC or HRA advise that you make any changes to your application before the review, please contact me to discuss before making these changes.
If you find you need to make any other changes to the submission please also let me know what these are before making the changes. Thanks for your co-operation with this.

Mr Dunstan Nicol-Wilson is the sponsor signatory for South London and Maudsley NHS Foundation Trust and will sign the sponsor declaration of your IRAS HRA application. Please find attached a guidance document for requesting electronic signatures for IRAS applications, the email to request Dunstan's signature is **slam-ioppn.research@kcl.ac.uk**.

Notice of change to the way in which applications are booked in for ethical review and/or NHS/HSC study wide review. A new online booking service has been rolled out for IRAS studies – replacing the previous Central Booking Service (CBS) telephone line. Please access the new online booking service via IRAS to book your application for review. Applicants making contact about fast-track COVID-19 studies, should continue to follow the current HRA guidance or email fast.track@hra.nhs.uk.

Please be advised that this application is not suitable for Proportionate Review and you should not select this option during your review.

When you have made the booking you will receive a confirmation email. You will need to enter some of the information from that email into the first page of the IRAS application – please do not amend any other part of the IRAS form or the sponsor and CI signatures will be invalidated.

Please could you copy our office into all of your correspondence with the REC and the HRA, forward to the R&D office a copy of the final documents submitted. We will contact you once the application is submitted to advise on how to obtain confirmation of NHS Trust capacity and capability.

For multi-site studies, your Facilitator will advise you how to formally contact the participating sites.

If you have any questions or encounter any problems with the submission please let me know.

Kind regards,

Regards, Dale.

Dale Batham
R&D Governance Facilitator
Joint R&D Office of South London and Maudsley NHS Foundation Trust (SLaM) and Institute of Psychiatry, Psychology & Neuroscience (IoPPN)
W1.12, Institute of Psychiatry, Psychology & Neuroscience (IoPPN),
King's College London, De Crespigny Park, London SE5 8AF
Dale.1.Batham@kcl.ac.uk / slam-ioppn.research@kcl.ac.uk

Please note that I work 3 days per week for IOPPN/SLaM.

Appendix 15 – FAST-R Service Feedback– CRISP study

NIHR | Maudsley Biomedical Research Centre

FAST-R Service Feedback

Date: 11/09/2020

Study Title: Clinical Response of Impulsivity after Brain Stimulation in Parkinson's disease

Submitted by: Arteen Ahmed

Consent Form

- The consent form is good but make sure the patients understand all of the long words and acronyms. When the form is a paper copy, I think the link at the bottom of page 2 won't be used. If it is online, it will be OK which you mention in the protocol.
- It needs to be clarified what exactly will be extracted from participants' NHS clinical records. A list of inclusions is given, but this list needs to be comprehensive.
- Detailed information on the relevant data protection legislations is also required.
- The meaning of 'incidental findings' needs to be given.
- Instead of "please initial" – it would be better if it said "please tick" each box if you agree with the statement.

Participant Information Sheet

As this is an information sheet for motor symptoms of Parkinson's disease, I think this information sheet is too difficult for them and too long.

Protocol

I think the protocol looks good but do a list of the acronyms and meanings so the reader can read it easily. I don't think you need a chart for the SAE reporting on page 21.

Good luck with your research. It might be good to look at other patient information sheets so you can see the language they use.

Many thanks for using FAST R Service. We hope you have found it useful and please do let us know if you need any more support or feedback.

The NIHR Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust & King's College London

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