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Characterising the Neuropsychological Profile of Psychotic Symptoms in Alzheimer's Disease and Imaging D2/3 Receptor Occupancy During Treatment

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**Characterising the Neuropsychological Profile of Psychotic
Symptoms in Alzheimer's Disease and Imaging D2/3 Receptor
Occupancy During Treatment**

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Thesis submitted for the degree of Doctor of Philosophy

**Institute of Psychiatry
King's College London**

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Abstract

Background

Psychotic symptoms occur in approximately 40% of patients with Alzheimer's disease (AD) and have been linked with striatal dopamine (D2/3) receptor function. The first component of the thesis aims to investigate the neuropsychological profile accompanying psychotic symptoms in AD, and establish whether cognitive and motor tasks which have a documented association with dopaminergic function might be markers of psychotic symptoms and delusional subtypes in AD. Dopamine D2/3 receptor occupancy studies have been instrumental in guiding antipsychotic prescribing in schizophrenia. The second part of the thesis aims to adapt [¹⁸F]fallypride imaging for use in healthy older people and in dopamine (D2/3) receptor occupancy studies in AD.

Methods

Neuropsychology: 70 AD subjects aged between 65 and 95 years were categorised into psychotic (n=34) and non-psychotic (n=36) groups, based on carer-rated scales, and then compared using a hypothesis-driven test battery.

Imaging: Eight healthy older (>65 years) adults were scanned twice, 4-6 weeks apart. [¹⁸F]fallypride binding potential (BP_{ND}) was determined and test-retest variability and intraclass correlation coefficient (ICC) values were calculated. A further six subjects with AD were recruited prior to commencing amisulpride treatment. [¹⁸F]fallypride BP_{ND} pre/post 2-8 weeks of amisulpride treatment and D2/3 occupancy was measured.

Results

Neuropsychology: Subjects with psychotic symptoms, in particular misidentification phenomena, had significantly poorer sustained attentional and visuoperceptual function.

Imaging: The adapted [¹⁸F]fallypride scanning protocol showed high reproducibility and reliability in all but the prefrontal regions and was generally well tolerated in AD subjects.

Conclusion

Neuropsychology: Sustained attention deficits may act as a marker of psychotic symptoms in AD due to associations with dopaminergic function in the associative striatum. Visuo-perceptual deficits may indicate additional pathology in the ventral visual stream, which could characterize the misidentification subgroup.

Imaging: The feasibility of an adapted scanning protocol was demonstrated in AD subjects and represents the first step towards defining a 'therapeutic window' of D2/3 occupancy to guide antipsychotic prescribing in AD.

Publications Arising From Thesis

Dunn J T, Clark-Papasavas C, Marsden P, Baker S, Cleij M, Kapur S, Kessler R, Howard R, Reeves S. Establishing the test–retest reliability of an adapted [¹⁸F]fallypride imaging protocol in older people (2013). *Journal of Cerebral Blood Flow & Metabolism* 33(7): 1098-1103.

Clark-Papasavas C, Dunn J T, Greaves S, Mogg A, Gomes R, Brownings, S, Liu K, Nwosu, B, Marsden P, Joemon J, Cleij M, Kessler R, Howard R, Reeves, S. Towards a therapeutic window of D2/3 occupancy for treatment of psychosis in Alzheimer's disease, with [¹⁸F]fallypride PET imaging. *The International Journal of Geriatric Psychiatry*. In Press.

Statement of Authorship

I can confirm that the collection, analysis, and interpretation of data in the current thesis is my own work and that all references have been cited accordingly. The original study design, in particular the timings of the adapted scanning protocol, was decided upon prior to my involvement in the research, by Dr Suzanne Reeves, Professor Robert Howard and their collaborators (Professor Robert Kessler and Professor Shitij Kapur). Informed consent for imaging subjects with Alzheimer's Disease was obtained by Dr Reeves.

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Table of Contents

TITLE PAGE	1
ABSTRACT	2
PUBLICATIONS ARISING FROM THESIS	4
STATEMENT OF AUTHORSHIP	5
ACKNOWLEDGEMENTS	6
TABLE OF CONTENTS	7
LIST OF TABLES	12
LIST OF FIGURES	14
LIST OF ABBREVIATIONS	16
CHAPTER 1: INTRODUCTION	19
1.1 ALZHEIMER'S DISEASE	19
1.1.1 Epidemiology	19
1.1.2 Diagnostic Criteria	20
1.1.3 Cognitive Deficits	23
1.1.4 Neuropsychiatric Deficits	25
1.1.5 Neurobiological changes contributing to cognitive and non-cognitive deficits in AD	26
1.2 THE DOPAMINERGIC SYSTEM	28
1.2.1 Neuroanatomy of Corticostriatal Neurocircuitry	28
1.2.2 Classification of Dopamine Receptors	30
1.2.3 Distribution of Dopamine Receptors	31
1.3 DOPAMINERGIC CONTROL OF MOVEMENT, COGNITION AND PSYCHOSIS IN AD	32
1.3.1 Role of Dopamine in Motor Control	32
1.3.2 Role of Dopamine in Cognitive Control	34
1.3.3 Role of Dopamine in Psychosis	35
1.4 AIMS OF THESIS: PART 1	37
1.5 TREATMENT OF PSYCHOTIC SYMPTOMS IN AD	38
1.5.1 Antipsychotic Medication: Mechanism of Action	38

1.5.2 Use of PET Imaging to Guide Antipsychotic Prescribing	38
1.5.3 Antipsychotic Sensitivity in AD	40
1.6 AIMS OF THESIS: PART 2	42
CHAPTER 2: OVERVIEW OF METHODOLOGY	44
2.1 NEUROPSYCHOLOGICAL PROFILE	45
2.1.1 Summary of Study Design	45
2.1.2 Recruitment and Screening	45
2.1.3 Ethical Approval	47
2.1.4 Sample Size Considerations	47
2.2 NEUROPSYCHOLOGICAL TESTING	47
2.2.1 Screening Tools	47
2.2.2 Hypothesis-Driven Tests	49
2.2.3 Neuropsychological Test Battery	50
2.2.4 Procedure for Administration of Neuropsychological Tests	54
2.3 STATISTICS	55
2.4 PART 2: PET IMAGING	55
2.4.1 Basic Principles of PET Imaging	55
2.4.2 Neuroreceptor Quantification	57
2.4.3 Compartmental Models	57
2.4.4 Radioligand Selection: [¹⁸ F]fallypride	61
2.5 METHODOLOGY FOR CHAPTER 4	62
2.5.1 Summary of Study Design	62
2.5.2 Recruitment and Screening	62
2.5.3 Scanning Protocol	63
2.5.4 Statistics	64
2.6 METHODOLOGY FOR CHAPTER 5	65
2.6.1 Summary of Study Design	65
2.6.2 Recruitment and Screening	65
2.6.3 Scanning Protocol	66
2.6.4 Amisulpride Dose-Titration	67
2.6.5 Monitoring Neuropsychiatric Symptoms and Motor Side Effects	68
2.6.6 Statistics	69

2.7 METHODOLOGY COMMON TO CHAPTERS 4 AND 5	69
2.7.1 Ethical Approval	69
2.7.2 Sample Size Considerations	70
2.7.3 PET Protocol	70
2.7.4 General Data Analysis	70
CHAPTER 3: ESTABLISHING THE NEUROPSYCHOLOGICAL PROFILE OF PSYCHOTIC SYMPTOMS IN AD	77
3.1 INTRODUCTION	77
3.1.1 Prevalence and Phenomenology	77
3.1.2 Pathophysiology of Psychotic Symptoms in AD	79
3.1.3 Cognitive Correlates of Psychotic Symptoms in AD	82
3.1.4 Psychosis Versus Delusional Subtypes	86
3.1.5 Aims	88
3.2 METHODS	89
3.2.1 Subjects	89
3.2.2 Neuropsychological Tests	89
3.2.3 Procedure	89
3.2.4 Statistics	89
3.3 RESULTS	91
3.3.1 Prevalence	91
3.3.2 Demographics	93
3.3.3 Neuropsychological Test Scores	94
3.3.4 Post-hoc Analyses of Psychotic Subgroups	100
3.3.5 Logistic Regression	104
3.4 DISCUSSION	105
3.4.1 Phenomenology	105
3.4.2 Hypothesis-Driven Tests	106
3.4.3 Neuropsychological Correlates of Psychotic Symptoms in AD	110
3.4.4 Logistic Regression	116
3.4.5 Limitations	116
3.5 CONCLUSION	119

CHAPTER 4: ESTABLISHING THE TEST-RETEST RELIABILITY OF AN ADAPTED [¹⁸F]FALLYPRIDE IMAGING PROTOCOL FOR USE IN OLDER PEOPLE	120
4.1 INTRODUCTION	120
4.1.1 Use of High Affinity Radiotracers to Image D2/3 Receptor Occupancy	120
4.1.2 Use of High Affinity Radiotracers to Image Endogenous Dopamine Release	121
4.1.3 [¹⁸ F]fallypride Imaging: Advantages and Limitations	122
4.1.4 Adapting [¹⁸ F]fallypride Imaging	123
4.1.5 Aims	124
4.2 METHODS	124
4.2.1 Scanning Protocol	124
4.2.2 Optimising the Protocol	124
4.2.3 Defining ROIs	125
4.2.4 Statistics	125
4.3 RESULTS	126
4.3.1 Mapping of PET images to ROI	126
4.3.2 Regional Uptake of [¹⁸ F]fallypride	129
4.3.3 Test-Retest Reproducibility of Regional [¹⁸ F]fallypride Binding	131
4.3.4 Reliability of Individual BP _{ND} Values	134
4.3.5 Regional Detectable Within-Subject % Change in [¹⁸ F]fallypride Binding	134
4.4 DISCUSSION	136
4.4.1 Consideration of Age-Related Factors in D2/3 PET Imaging	136
4.4.2 Suitability for Occupancy Studies	137
4.4.3 Suitability for Dopamine Release Studies	138
4.4.4 Potential Limitations	140
4.5 CONCLUSION	141
CHAPTER 5: OPTIMISING [¹⁸F]FALLYPRIDE IMAGING FOR D2/3 OCCUPANCY STUDIES IN AD	142
5.1 INTRODUCTION	142
5.1.1 Antipsychotic Sensitivity in the Elderly: Mechanisms	142
5.1.2 Directly Assessing the Mechanisms of Heightened Sensitivity: Use of D2/3 Occupancy Studies	145

5.1.3 Aims	146
5.2 METHODS	147
5.2.1 Pre-Treatment Protocol	147
5.2.2 Post-Treatment Protocol	147
5.2.3 Optimising the Protocol	147
5.2.4 Defining ROIs	148
5.2.5 Movement Correction	148
5.2.6 Statistics	149
5.3 RESULTS	149
5.3.1 Clinical and Demographic	149
5.3.2 Regional D2/3 Receptor Binding	154
5.3.3 Regional D2/3 Receptor Occupancy	156
5.4 DISCUSSION	162
5.4.1 Dose-Occupancy Relationships	163
5.4.2 Methodological Issues	164
5.4.3 Accuracy of Post-Treatment Protocol	165
5.5 CONCLUSION	166
CHAPTER 6: FINAL DISCUSSION	167
6.1 SUMMARY OF MAIN FINDINGS	167
6.1.1 Establishing the Neuropsychological Profile of Psychotic Symptoms in AD	167
6.1.2 Establishing the Test-Retest Reliability of an Adapted [¹⁸ F]fallypride Imaging Protocol for Use in Older People	169
6.1.3 Optimising [¹⁸ F]fallypride Imaging for D2/3 Occupancy Studies in AD	170
6.2 LIMITATIONS	171
6.2.1 Sampling	171
6.2.2 Neuropsychological Test Measures	173
6.2.3 Image Analysis: MRI and Partial Volume Effects	175
6.3 IMPLICATIONS OF FINDINGS AND DIRECTIONS FOR FUTURE RESEARCH	176
6.3.1 Neuropsychological Test Battery	176
6.3.2 Imaging	177
REFERENCES	180
APPENDIX	221

List of Tables

Table 1.1:	
Summary of ICD-10 and DSM-IV Diagnostic Criteria for AD	21
Table 1.2:	
Summary of NINCDS-ADRDA Diagnostic Criteria for Probable AD	22
Table 3.1:	
Description of Delusional Content in AD	79
Table 3.2:	
Classification of Delusions	92
Table 3.3:	
Psychotic Subgroups	93
Table 3.4:	
Demographics	94
Table 3.5.1:	
Motor Speed - Analysis of Covariance	95
Table 3.5.2:	
Sustained Attention - Analysis of Covariance	95
Table 3.5.3:	
Executive Function - Multivariate Analysis of Covariance	96
Table 3.5.4:	
Memory - Multivariate Analysis of Covariance	97
Table 3.5.5:	
Language - Analysis of Covariance	97
Table 3.5.6:	
Constructional Praxis - Multivariate Analysis of Covariance	98
Table 3.5.7:	
Visuoperceptual Function – Multivariate Analysis of Covariance	99
Table 3.5.8:	
Visuoperceptual Function - Posthoc Pairwise Comparisons	100
Table 3.6.1:	
Sustained Attention – Subgroup Analysis of Covariance	101
Table 3.6.2:	
Sustained Attention – Posthoc Pairwise Comparisons	101

Table 3.6.3:	
Visuoperceptual Function – Subgroup Multivariate Analysis of Covariance	102
Table 3.6.4:	
Visuoperceptual Function – Between Subjects Effects	103
Table 3.6.5:	
Visuoperceptual Function – Posthoc Pairwise Comparisons	103
Table 3.7:	
Logistic Regression	104
Table 4.1:	
Test-Retest Reproducibility of Regional [¹⁸ F]fallypride Binding Using Method 1	132
Table 4.2:	
Test-Retest Reproducibility of Regional [¹⁸ F]fallypride Binding Using Method 2	133
Table 4.3:	
Mean COV Across Subjects for Individual ROIs	134
Table 5.1:	
Bias Corrected Pre-Treatment BP _{ND}	150
Table 5.2:	
Clinical and Demographic data	151
Table 5.3:	
Pre-Treatment Scan: Percentage Change in [¹⁸ F]fallypride BP _{ND} Between Method 1 and Method 2	154
Table 5.4:	
Post-Treatment Scan: Percentage Change in [¹⁸ F]fallypride BP _{ND} Between Method 1 and Method 2	155
Table 5.5:	
Regional Dopamine D2/3 Receptor Occupancy During Treatment With Amisulpride 50mg Daily: Comparison of Method 1 and Method 2	161

List of Figures

Figure 1.1:	
Parallel Loop Model	29
Figure 1.2:	
The Direct and Indirect Pathways of Motor Control	33
Figure 1.3:	
Therapeutic Window of D2/3 Receptor Occupancy for Antipsychotics in Young Adults	40
Figure 1.4:	
Mechanisms of Antipsychotic Sensitivity in the Elderly	43
Figure 2.1:	
Principles of PET Imaging	56
Figure 2.2:	
The Three Compartment Model	59
Figure 2.3:	
Regional Time-Activity Curve of [¹⁸ F]fallypride Uptake Over 180 minute Scanning Session	64
Figure 2.4:	
Flow Diagram of Pre-Processing Method	75
Figure 2.5:	
Delineation of Striatal Functional Subdivisions	76
Figure 3.1:	
Classification of Psychotic Symptoms in AD	78
Figure 3.2:	
Proposed Pathogenesis of Delusions Arising From Limbic System Dysfunction	81
Figure 3.3:	
Increased Striatal D2/3 Receptor Availability Associated with Delusions in AD	82
Figure 3.4:	
Scatter Plot Showing Correlation Between Striatal [¹¹ C] RAC Binding and Performance on Motor Latency Task	85
Figure 3.5:	
Scatter Plot Showing Correlation Between Striatal [¹¹ C] RAC Binding and Performance on RVP Task	85

Figure 4.1:	
Alignment of Striatal ROIs with an Individual's PET Scan	127
Figure 4.2:	
Alignment of Extrastriatal ROIs with an Individual's PET Scan	128
Figure 4.3:	
Time-Activity Curves (Method 1) Representing [¹⁸ F]fallypride Uptake in All ROIs in a Single Subject	129
Figure 4.4:	
Time-Activity Curves (Method 1) Representing [¹⁸ F]fallypride Uptake in Striatal Subdivisions in a Single Subject	130
Figure 4.5:	
Time-Activity Curves (Method 1) Representing [¹⁸ F]fallypride Uptake in Extrastriatal ROIs in a Single Subject	130
Figure 4.6:	
Regional Detectable % Change in [¹⁸ F]fallypride Binding Using Method 1 and Method 2	135
Figure 5.1:	
Proposed Mechanisms of Antipsychotic Sensitivity	143
Figure 5.2:	
Time-Activity Curves for the Caudate, Showing 60-Second Frames Removed From Each Scanning Session	153
Figure 5.3:	
Parametric Image of [¹⁸ F]fallypride Binding Pre and Post Amisulpride	156
Figure 5.4:	
Time-Activity Curves Showing Striatal D2/3 Receptor Occupancy	158
Figure 5.5:	
Time-Activity Curves Showing Striatal Subdivisions D2/3 Receptor Occupancy	159
Figure 5.6:	
Time-Activity Curves Showing Extrastriatal D2/3 Receptor Occupancy	160

List of Abbreviations

AA	Alzheimer's Association
ACC	Anterior Cingulate Cortex
AC	Attenuation Corrected
AC-PC	Anterior Commissure – Posterior Commissure
AD	Alzheimer's Disease
ANCOVA	Analysis of Covariance
ADHD	Attention deficit hyperactivity disorder
APA	American Psychiatric Association
ARSAC	Administration of Radioactive Substances Advisory Committee
BBB	Blood Brain Barrier
BP _{ND}	Binding Potential (Non-Displaceable)
BPSD	Behavioural and Psychological Symptoms of Dementia
Bq	Becquerel
[¹¹ C] RAC	[¹¹ C]Raclopride
cAMP	Adenosine 3',5'-monophosphate
CANTAB	Cambridge Neuropsychological Test Automated Battery
CASI	Cognitive Assessment Screening Instrument
CBRS	CERAD Behavioural Rating Scale
CDR	Clinical Dementia Rating Scale
CERAD	The Consortium to Establish a Registry for Alzheimer's Disease
ChEI	Cholinesterase Inhibitor
CNS	Central Nervous System
COV	Coefficient of Variation
CT	Computerised Tomography
DLB	Dementia with Lewy Bodies
DRS	Dementia Rating Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPS	Extrapyramidal Symptoms
FAB	Frontal Assessment Battery

FAQ	Functional Assessment Questionnaire
FBP	Filtered Back Projection
FDA	Food and Drug Administration
FDOPA	[¹⁸ F]fluoro-L-dopa
GDS-15	Geriatric Depression Scale
GDS	Global Deterioration Scale
GPe	External Globus Pallidus
GPi	Internal Globus Pallidus
[¹²³ I]IBZM	[¹²³ I]Iodobenzamide
ICC	Intraclass Correlation Coefficient
ICD	International Classification of Diseases
ISI	Interstimulus Interval
ITG	Inferior Temporal Gyrus
LSD	Least Significant Difference
MANCOVA	Multivariate Analysis of Covariance
MAO-B	Monoamine Oxidase B
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MOT	Motor Screening Task
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribo Nucleic Acid
MTG	Middle Temporal Gyrus
NAC	Non-attenuation corrected
NART	National Adult Reading Test
NIA	National Institute of Aging
NIH	National Institute of Health
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
OFC	Orbitofrontal Cortex
6-OHDA	6-Hydroxydopamine
PD	Parkinson's Disease

PET	Positron Emission Tomography
ROI	Region-of-Interest
RVP	Rapid Visual Processing
SAS	Simpson Angus Scale
SD	Standard Deviation
SE	Standard Error
SLaM	South London and Maudsley
SNc	Substantia Nigra (pars compacta)
SPECT	Single Photon Emission Computed Tomography
SPM	Statistical Parametric Mapping
SRT	Simple Reaction Time
STN	Subthalamic Nucleus
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
VOSP	Visual Object and Space Perception
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organisation

Chapter 1: Introduction

This thesis investigates psychotic symptoms in Alzheimer's disease (AD), with a focus on neuropsychology and imaging. The first component of the thesis aims to investigate the neuropsychological profile of psychotic symptoms in AD, and establish if test performance measures which have an established association with dopaminergic function might act as 'cognitive markers' of psychotic symptoms in AD. The second component aims to adapt [¹⁸F]fallypride Positron Emission Tomography (PET) imaging for use in healthy older people and in dopamine (D2/3) receptor occupancy studies in AD. This chapter is structured as follows:

- 1.1 The first section provides a general overview of AD, including epidemiology, diagnostic criteria, and cognitive and non-cognitive changes associated with the disease.
- 1.2 The second section discusses the general anatomy of the dopaminergic system, including corticostriatal neurocircuitry, and the classification and distribution of receptor subtypes.
- 1.3 The third section details the role of dopamine in cognition, motor function and psychotic symptoms in AD.
- 1.4 The fourth section outlines the aims for the neuropsychological component of this thesis.
- 1.5 The fifth section discusses the heightened sensitivity to antipsychotic drugs in AD, and the use of PET imaging in guiding treatment strategies.
- 1.6 The final section outlines the aims for the imaging component of this thesis.

1.1 Alzheimer's Disease

1.1.1 Epidemiology

Dementia is an umbrella term used for a range of neurodegenerative diseases, which result in deterioration of cognitive abilities. AD is the most common type of dementia, accounting for 50-60% of all cases (Blennow et al., 2006). The prevalence of AD demonstrates an almost exponential increase with age; below 1% of those aged 60-64 are affected, in comparison to a prevalence of between 24% and 33% in those aged above 85 years in the western world (Ferri et al., 2005). In 2010 it was

estimated that 36 million people were suffering with dementia globally. Due to the anticipated increase in life expectancy, this number is predicted to almost double in the next 20 years, and more than triple to an estimated 115 million by 2050 (World Alzheimer Report 2012). AD is characteristically a progressive illness, resulting in death after 10-15 years from the time of onset, and a median of 6 years from the time of diagnosis (Waring et al., 2005). The progressive deterioration in both cognitive function and the accompanying non-cognitive symptoms are the pre-requisite for growing demands on the health and social care system, causing a large economic burden. The World Alzheimer Report 2010 estimated the total worldwide costs of dementia to amount to \$604 billion (US), with an annual cost of £23 billion in the UK alone (Alzheimer's Society Dementia 2012 report). Costs accumulate due to informal care, social care and direct medical expenses.

1.1.2 Diagnostic Criteria

Attempts to establish diagnostic criteria for AD began in 1952, with the release of the first Diagnostic and Statistical Manual (DSM-1) (American Psychiatric Association (APA), 1952). In this first edition, AD was not specified, but instead referred to as an 'organic brain syndrome', which included all neurodegenerative disorders causing dementia. It was not until 1980, with the release of the third revision of the DSM (DSM-III), that the term AD was included to describe the main cause of 'senile' age-related dementia (APA, 1994). Subsequent revisions led to the widely used DSM-IV criteria, with the fifth and most recent edition published earlier this year (May 2013). Another diagnostic manual was devised by the World Health Organisation (WHO, 1992), named the International Classification of Diseases (ICD). The ICD was developed alongside the DSM, with largely similar codes being used for the two manuals (summarised in Table 1.1). The ICD is currently in its tenth edition (ICD-10), with international survey results suggesting it is more commonly used for clinical diagnosis, in contrast to the DSM which is more valued for research purposes. The most commonly used criteria for research however, is that developed by the combined efforts of the National Institute of Health (NIH), the National Institute of Neurological and Communicative Disease and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al.,

1984) (Table 1.2). This criterion is more detailed than those mentioned above, differentiating between possible, probable and definite AD. In 2011, the NINCDS-ADRDA was revised for the first time in 27 years, to outline new guidelines for both the clinical diagnosis of, and research into, AD (McKhann et al., 2011). In contrast to the original criteria which only described the later stages of the disease, the new guidelines cover the full spectrum of the illness, differentiating between three stages; preclinical, mild cognitive impairment, and a final stage of AD. In addition, the new guidelines recognise the importance of biomarkers (measures in blood, fluid, or imaging) to detect the preclinical stages of the disease, prior to the onset of symptoms. The revised criteria were developed by the National Institute of Aging (NIA) and the Alzheimer's Association (AA).

Table 1.1: Summary of ICD-10 and DSM-IV Diagnostic Criteria for AD

Fulfil criteria for dementia syndrome:

- multiple cognitive deficits, which must include amnesia
- functional impairment
- clear consciousness
- change from previous level of functioning
- long duration (at least 6 months)

Insidious Onset

Gradual progression

Absence of focal neurological signs

Absence of systemic or brain disease sufficient to cause dementia

(APA 1994; WHO 1992)

Table 1.2: Summary of NINCDS-ADRDA Diagnostic Criteria for Probable AD

Dementia

(established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests)

Deficits in two or more areas of cognition

Progressive worsening of memory and other cognitive functions (such as language, motor skills and perception)

No disturbance of consciousness

Onset between age 40 and 90

Absence of systemic disorders or other brain diseases that in and of themselves could account for progressive deficits in memory and cognition

Note: Patients who meet the above criteria (McKhann et al., 1984) would also meet the revised NINCDS-ADRDA criteria for probable AD (McKhann et al., 2011).

A clinical diagnosis of AD is generally made following a referral by a general practitioner to a specialist service, where a cognitive and functional assessment will be carried out, together with a physical examination. A detailed, focused history is also obtained from an informant. Blood tests are routinely carried out to exclude other potentially reversible causes of memory loss, such as vitamin B12 deficiency or hypothyroidism. Structural imaging in the form of CT (Computerised Tomography) or MRI (Magnetic Resonance Imaging) is also performed to exclude the presence of a stroke, normal pressure hydrocephalus, or space occupying lesion. The screening measures most widely used in the assessment procedure include the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), which is a global measure of cognition including five domains: orientation, language, memory, attention and praxis. The test is scored out of 30, with scores of 26 suggesting a questionable dementia, 21-26 a mild dementia, 11-20 a moderate dementia, and below 10 a severe dementia (Folstein et al., 2001). Non-cognitive symptoms are rated by an informant, using scales such as the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), which measures the frequency and severity of 12 behaviours commonly associated with AD, including neuropsychiatric symptoms: delusions, hallucinations, apathy, agitation, disinhibition, depression, irritability, elation, anxiety, and aberrant motor behaviour; and neurovegetative symptoms: night time behaviour and appetite. Additional screening measures include: The Functional

Assessment Questionnaire (FAQ) (Pfeffer et al., 1982), used to assess the ability to carry out tasks of daily living, and the Global Deterioration Scale (GDS) (Reisberg et al., 1982) and Clinical Dementia Rating scale (CDR) (Berg 1988), both of which measure the progression of the disease and include cognitive, functional and neuropsychiatric domains.

1.1.3 Cognitive Deficits

AD is characterised by pathology in the medial temporal lobe (e.g. hippocampus, and entorhinal cortex), a region critical for episodic memory (Braak & Braak 1991). Therefore, impaired episodic memory, characterised by a reduced ability to remember new information, is the most prominent symptom of AD, and is listed in both the DSM-V and ICD-10 diagnostic criteria (WHO 1992; APA 1994). Such symptoms typically occur early in the disease course (Butters et al., 1987; Salmon & Bondi 2009), and can include frequent repetition of questions, forgetting names and appointments, or mislaying household items. In contrast, distant memories are relatively well preserved in mild AD (Beatty et al., 1988). As the disease progresses however, memory loss broadens to include older events, and other cognitive domains begin to show impairments, including semantic memory, language, attention, executive function and visuospatial abilities, discussed below.

Attention and executive function are well characterised symptoms of AD (Perry & Hodges 1999), and have been reported to be the first non-memory domains to manifest in AD (Binetti et al., 1996; Lafleche & Albert 1995). Advances in research have led to the fractionation of attention into separate components, which include ‘selective attention’ (the ability to attend to relevant stimuli, whilst screening out irrelevant stimuli), ‘divided attention’ (the ability to attend to more than one stimuli simultaneously) and ‘sustained attention’ (the ability to focus on one task for unbroken periods of time) (Posner & Petersen 1990). Whilst research has shown impairments in both divided and certain aspects of selective attention (mainly set-shifting and response selection) in mild AD, there is a general consensus that sustained attention remains fairly intact, at least in the early stages (Perry & Hodges 1999). This is supported by the normal performance of patients with mild AD on tests of immediate attention span, compared with supra-span tests (Cherry et al.,

2002). However this is not agreed by all, with some reporting increased vigilance decrements in mild AD compared to healthy controls (Berardi et al., 2005).

Executive function involves higher order cognitive processes, which help to plan and monitor sequences of actions. Executive deficits are apparent in AD in the form of difficulties with everyday tasks such as planning and cooking a meal, travelling to a new location, or choosing the appropriate clothes to wear. Neuropsychological tests of executive function are difficult to interpret, as many involve aspects of attention. However, impairments in performance on several tasks thought to measure executive function to a greater degree (Patterson et al., 1996), such as the Porteus Maze test (requiring foresight and planning), and part B of the trail-making test (requiring concurrent manipulation of information), provide evidence of executive deficits early in the course of AD (Grady et al., 1988). Other tests involving the problem solving aspect of executive function, such as the Tower of London puzzle (Lange et al., 1995) and the modified Wisconsin Card Sorting Task (Bondi et al., 1993), are also impaired in mild AD patients compared to healthy age-matched controls. Specifically, the greatest executive deficits in AD are reported in tasks which involve set-shifting and sequencing and monitoring of information, for which the simultaneous processing of information is required (Lafleche & Albert 1995). Another component of executive function is 'working memory', which refers to a process whereby information that is the immediate focus of attention is temporarily held in a limited-capacity immediate memory buffer, while being manipulated by a 'central executive' (Baddeley 2003). Studies of working memory performance in AD suggest deficits are initially mild, perhaps disrupting the central executive only, and not the immediate memory. However, as the disease progresses, both components of the working memory system are disrupted, resulting in more severe deficits (Baddeley et al., 1991; Collette et al., 1999).

Language deficits are reported in AD and appear to progress in parallel with disease severity (Emery 2000). Semantic impairment occurs early in the disease course, affecting performance on confrontational naming tasks and verbal fluency (Groves-Wright et al., 2004). A deterioration of semantic memory is thought to result in many of the language difficulties seen in AD, such as word finding difficulties, reduced number of words, and content word substitutions or omissions in written language (Henderson et al., 1992; Horner et al., 1988; Neils et al., 1989). Support for the

involvement of semantic impairment in the early stages of the disease is provided by the ability of a word fluency task (semantic) to differentiate between mild-AD and healthy controls (Groves-Wright et al., 2004). Phonological difficulties and simpler grammatical structures are reported as the disease progresses, together with a worsening in spelling performance (Hughes et al., 1997; Kemper et al., 1993; Kempler et al., 1998). In a study comparing a range of language abilities between healthy controls and patients with mild-AD and moderate-AD, the moderate AD group were significantly worse than both other groups on all tasks of written and verbal language, and showed greater variability in performance. These results suggest that language deficits predominantly occur later in the disease course, and individuals are affected with different profiles of deficits (Groves-Wright et al., 2004).

Visuospatial deficits are also reported to occur in AD, and can be observed in various tasks such as drawing (Ober et al., 1991), copying (Brouwers et al., 1984) and construction (Johnson et al., 1997). It has been suggested that visuoperceptual abilities are impaired in early AD (Alegret et al., 2009; Binetti et al., 1998), while constructional impairments become apparent later in the disease course (Binetti et al., 1998).

Other common cognitive deficits in AD include apraxia; the inability to carry out complex motor tasks (Dumont et al., 2000), and agnosia; the inability to recognise objects or faces (Goudour et al., 2011).

1.1.4 Neuropsychiatric Deficits

The non-cognitive symptoms of AD are generally classified into two domains; neuropsychiatric symptoms, which include agitation, apathy, disinhibition, irritability, aberrant motor behaviour, psychosis, depression, anxiety and elation; and neurovegetative symptoms, which relate to sleep and appetite disturbances. The umbrella term 'Behavioural and Psychological Symptoms of Dementia' (BPSD) (Finkel et al., 1996) is typically used to describe the non-cognitive symptoms of dementia, which occur in an estimated 90% of patients (Lyketsos et al., 2002). In the past, such symptoms have received less attention than the well documented cognitive deficits. However, their importance is becoming increasingly recognised given the

association with increased carer distress (Deimling & Bass 1986), earlier institutionalisation (Steele et al., 1990), more rapid cognitive decline (Ropacki & Jeste 2005), and poorer quality of life for the patient and carer (Banerjee et al., 2006; Matsui et al., 2006). In addition, BPSD contribute significantly to the overall costs of dementia care (Beeri et al., 2002; Herrmann et al., 2006).

It has been observed that BPSD tend to occur in clusters rather than in isolation, and a number of broad groupings have been identified by factor analytical studies which have used rating scales designed to measure such symptoms. Comparison between studies is difficult however, especially given that many did not differentiate between the different aetiologies of dementia. Factor analysis of BPSD in AD has shown several distinct factors relating to aggression, affect, psychotic symptoms, and frontal lobe dysfunction (disinhibition and activity disturbance) (Cerejeira et al., 2012). Many of the studies are limited by their small sample sizes and are difficult to compare due to differences in assessment measures and study design. Nevertheless, a certain degree of concordance between studies does exist, particularly in relation to delusions and hallucinations, which have been grouped into a ‘psychosis factor’ in all factor analytical studies using the NPI (a rating scale used to assess BPSD). The grouping of delusions and hallucinations is supported by the existence of a separate diagnostic criteria, which identifies psychosis as a distinct syndrome in AD (Jeste & Finkel 2000). It is thought that by identifying discrete subgroups of neuropsychiatric symptoms in AD, the recognition of such symptoms and clinical treatments could be improved, based on the fact that the co-occurrence of symptoms may represent discrete biological underpinnings. The present thesis addresses psychotic symptoms in AD, with a particular focus on the role of the neurotransmitter dopamine as a possible biological substrate.

1.1.5 Neurobiological changes contributing to cognitive and non-cognitive deficits in AD

Since the 1970s, the ‘cholinergic hypothesis’ has been the predominant theory underlying the cognitive symptoms in AD. The cholinergic hypothesis was derived from post-mortem studies of AD patients, which found a significant reduction in the activity of enzymes involved in the synthesis and degradation of acetylcholine

(Bowen et al., 1976; Davies & Maloney 1976). The theory attributes the marked memory and learning deficits in AD to acetylcholine loss. Later, lesion and pharmacological challenges in experimental animals showed a crucial effect of cholinergic neurotransmission on other cognitive symptoms of AD, including attentional performance, discrimination learning and avoidance learning and habituation (Collerton 1986; Sutherland et al., 1982; Wishaw IQ 1985). More recently, pharmacological studies using Cholinesterase Inhibitors (ChEI) in patients with AD have shown improved performance on a choice reaction time task and visual selective attention task, compared to those taking placebo (Caramelli et al., 2004; Foldi et al., 2005; Gorus et al., 2007; Sahakian & Coull 1993; Vellas et al., 2005).

In 1998, Cummings and Back suggested that the cholinergic hypothesis may also underpin BPSD, in particular psychotic symptoms (Cummings & Back 1998). This theory is predominantly based on pharmacological studies, which have demonstrated a reduction/amelioration of delusions following treatment with ChEIs or muscarinic agonists (Bodick et al., 1997; Cummings et al., 1993; Kaufer et al., 1996; Paleacu et al., 2002; Raskind et al., 1997). Further evidence for a role of cholinergic neurotransmission in psychosis is provided by the fact that delusions correlate with regions showing marked cholinergic deficits, including the temporal and frontal lobes (Kotrla et al., 1995; Mentis et al., 1995; Starkstein et al., 1994; Sultzer et al., 1995; Procter et al., 1988).

However, some authors argue that cholinergic deficits alone may not be enough to explain the cognitive and non-cognitive symptoms of AD, and suggest that perturbation of the dynamic balance between acetylcholine and other neurotransmitters, such as serotonin (Garcia-Alloza et al., 2005), and/or dopamine (Cummings et al., 2011), may play a crucial role (Dringenberg 2000; Cummings et al., 2011; Garcia-Alloza et al., 2005).

The present thesis will focus on the role of dopamine as a possible biological substrate of motor, cognitive and neuropsychiatric control in AD. In AD, dopamine transmission is relatively preserved (Cummings et al., 2011, Piggott et al., 1999) in contrast to the well documented cholinergic deficits (reviewed by Francis et al., (1999)). Therefore, dopamine is likely to maintain its role in motor control and cognition, and may contribute to the formation of psychotic symptoms. An overview

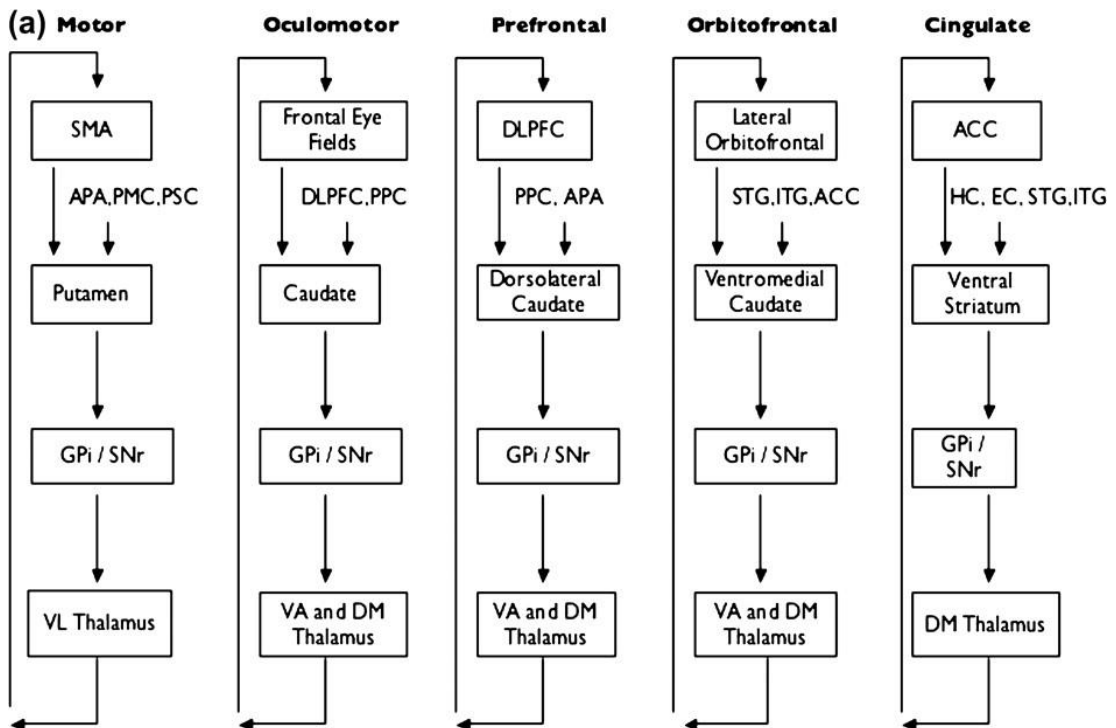
of the dopaminergic system is given in Section 1.2, followed by a description of its role in motor control, cognition and psychotic symptoms in Section 1.3.

1.2 The Dopaminergic System

1.2.1 Neuroanatomy of Corticostriatal Neurocircuitry

The striatum receives the densest dopaminergic innervation in the mammalian brain, with afferents arising from neurons in the substantia nigra and the ventral tegmental area of the midbrain (Andén et al., 1966; Björklund et al., 1984). Initially, the role of dopamine in the striatum was thought to be limited solely to motor control, given the movement deficits observed in Parkinson's disease (PD) following nigrostriatal dopaminergic denervation (Hornykiewicz & Kish 1987). The role of the basal ganglia in motor control soon became apparent, with early evidence suggesting that the basal ganglia received striatal inputs from the entire cerebral cortex, which were integrated via the ventrolateral thalamus, and projected back to the motor cortex (Allen & Tsukahara 1974; Evarts & Thach 1969; Kemp & Powell 1971). However, later evidence suggested that two distinct loops pass through the basal ganglia, one 'motor' loop, which receives inputs from the sensorimotor cortex and projects to premotor areas, and one 'association' loop, which receives inputs from the association areas and projects to portions of the prefrontal cortex (DeLong & Georgopoulos 1981). Further research led to the suggestion of four additional circuits organised in parallel with the motor circuit. Each circuit engages specific regions of the cerebral cortex, which project through the basal ganglia to the thalamus, and back to a specific region of the cortex. The five proposed basal ganglia-thalamocortical circuits are illustrated in Figure 1.1.

Figure 1.1: Parallel Loop Model



(Postuma & Dagher 2006)

The existence of multiple closed loop circuits was confirmed by Middleton and Strick, who used the retrograde transneuronal transport of the herpes simplex virus type 1 (HSV1) to trace the circuitry of the central nervous system (CNS) in primates, and therefore map the basal ganglia projections (Middleton & Strick 2000). The anatomy of the fronto-striato-thalamic loops supports a role for dopamine in cognitive and emotional processes, as well as motor control, and is discussed later in this chapter.

There are differing views as to the organisation of corticostriatal connectivity. Some authors have suggested that each cortical region is projected in a strict topographical manner to the striatum, and that each striatal region receives projections from the nearest cortical area (Kemp & Powell 1970). However, given that non-adjacent cortical areas (e.g. prefrontal and parietal cortices) project to adjacent striatal territories (Selemon & Goldman-Rakic 1985), others have argued against a topographical organisation and instead proposed a tripartite functional division of the striatum into motor, associative, and limbic areas (Parent 1990). The 3 subdivisions include: associative striatum (consisting of the rostral putamen and most of the head

of the caudate), which receives its densest input from the dorsolateral prefrontal cortex; sensorimotor striatum (consisting of the caudal and dorsolateral putamen and dorsolateral rim of the caudate), which receives input from motor and premotor cortices; and limbic striatum (consisting of the ventral caudate and putamen, including the nucleus accumbens), which receives projections from the orbital and medial frontal cortex. The differences in anatomical connections reflect the distinct functional subdivisions of this model, whereby the associative striatum is involved in attention and executive control (Selemon & Goldman-Rakic 1985), the sensorimotor division is involved in motor control and coordination (Flaherty & Graybiel 1994), and the limbic striatum plays a role in motivational and reward processes (Kunishio & Haber 1994). The tripartite subdivision model is consistent with the parallel loop theory (Alexander et al., 1986), which proposed multiple segregated circuits conveying either sensorimotor (motor and oculomotor loops), associative (dorsolateral prefrontal and lateral orbitofrontal loops) or limbic (anterior cingulate loop) information (Alexander & Crutcher 1990). However, the tripartite functional organisation of the cortico-striatal projections does not imply further functional subdivisions within each striatal region, as proposed by the parallelist view.

1.2.2 Classification of Dopamine Receptors

Adenosine 3',5'-monophosphate (cyclic AMP) is a second messenger molecule, involved in intracellular signal transduction, and is activated by the enzyme adenylyl cyclase (McAfee et al., 1971). Dopamine receptors were initially thought to exist as two discrete subtypes, one which is positively coupled to adenylyl cyclase, and one independent of cAMP. The two subtypes were identified as D1 and D2 receptors, respectively (Kebabian & Calne 1979). After about a decade, the introduction of gene cloning procedures identified three new subtypes of receptors, which were named D3 (Sokoloff et al., 1990), D4 (Van Tol et al., 1991) and D5 (Sunahara et al., 1991). However, it was later suggested that all the receptor subtypes fall into the two initial classifications, referred to as D1-like (D1, D5) and D2-like (D2, D3, D4) (Missale et al., 1998). There are significant structural and ligand binding characteristics within each receptor family, for example a 75% homology between the transmembrane domains of D2 and D3 receptors (Missale et al., 1998). This is

reflected in reports from pharmacological studies which demonstrate D3 receptors to bind to D2-selective ligands with relatively high affinity (Seeman & Van Tol 1994). An example of this would be the use of D2-selective radiotracers used in PET imaging, which are unable to differentiate between the two receptors. As a result, such tracers are referred to as D2/3 receptor tracers, and the possibility of D3 binding cannot be excluded in the interpretation of results.

1.2.3 Distribution of Dopamine Receptors

Given the absence of ligands specific to each receptor subtype, the distribution of dopamine receptor messenger (m)RNA has been studied using in situ hybridisation. D2 receptor mRNA is present in all major brain regions receiving dopaminergic projections, but is predominantly expressed in the striatum (Bouthenet et al., 1991). D2 receptor mRNA is highly expressed in the cell bodies of dopamine neurons in the substantia nigra and ventral tegmental area. This suggests an additional role of D2 receptors in modulating dopaminergic transmission through pre-synaptic autoreceptors, and is supported by studies of mice lacking the D2 receptor gene (Dickinson et al., 1999; Mercuri et al., 1997). In contrast to the widespread distribution of D2 dopamine receptors, D3 receptors have a more restricted distribution, with mRNA primarily being expressed in limbic regions, in particular the nucleus accumbens (ventral striatum) (Bouthenet et al., 1991). D3 receptor mRNA is poorly expressed in the dorsal striatum. The different distributions of the two receptors may help to interpret data from imaging studies which have used D2/3 receptor radiotracers.

Of the other receptor subtypes, D1 receptors are the most widely distributed and the most abundant of the receptor subtypes, with the highest levels of mRNA detected in the caudate, putamen, nucleus accumbens, and olfactory tubercle. Cells expressing D1 receptor mRNA were also detected in the cerebral cortex, limbic system, hypothalamus, and thalamus (Fremeau et al., 1991).

D4 receptor mRNA is found in many brain regions, including the frontal cortex, amygdala, hippocampus, hypothalamus, pituitary and the retina (Cohen et al., 1992; Van Tol et al., 1991), albeit at lower levels than D1 and D2 receptors. The

distribution of D5 receptors has been more difficult to measure, due to the similarities between dopamine D1 and D5 sequences (Sunahara et al., 1991).

1.3 Dopaminergic Control of Movement, Cognition and Psychosis in AD

1.3.1 Role of Dopamine in Motor Control

Overview

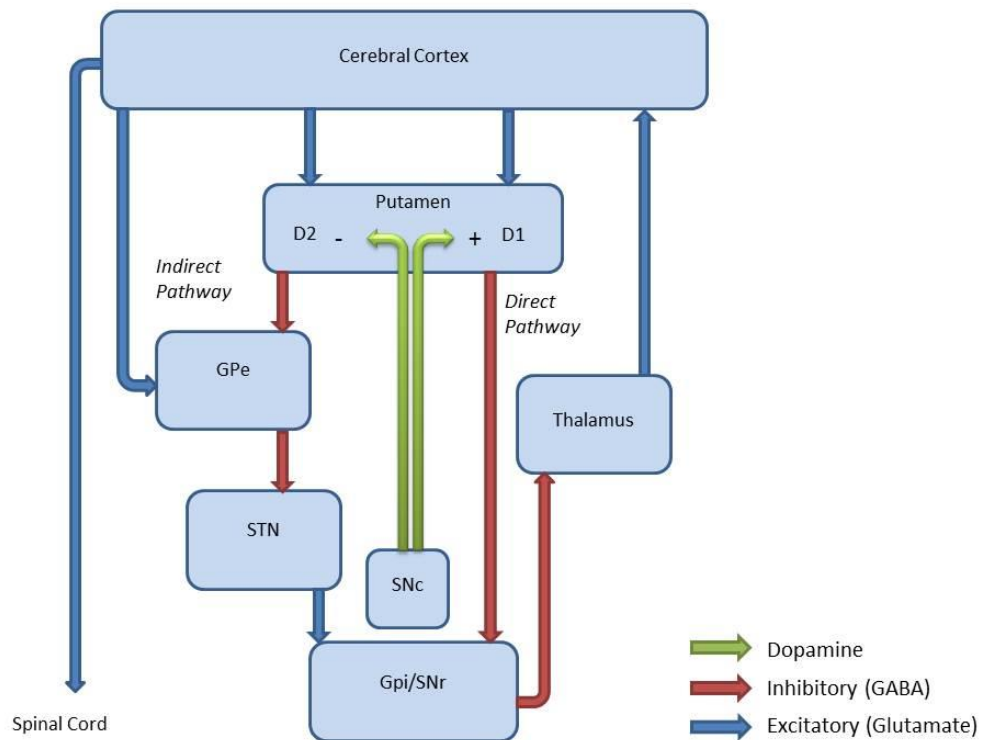
The role of the dopaminergic system in movement control has been well documented since the initial finding that nigrostriatal dopamine loss was responsible for the motor deficits seen in patients with PD (Bernheimer & Hornykiewicz 1965). Of the basal ganglia-thalamocortical circuits, the motor loop has been the most extensively studied, due to its importance in motor disorders, such as PD and Huntington's disease (Wichmann & DeLong 1996). Research has identified two pathways in the control of movement through the basal ganglia; the direct and indirect pathways (illustrated in Figure 1.2). Dopaminergic input from the substantia nigra pars compacta (SNc) induces excitation in the direct pathway, via activation of dopamine D1 receptors, and inhibition in the indirect pathway via D2 receptors. The direct pathway facilitates movement by decreasing inhibitory output from the internal globus pallidus (GPi) to the thalamus, while the indirect pathway suppresses movements by increasing the inhibitory outputs of the basal ganglia. Disruption of the dopaminergic system therefore deregulates the circuit, resulting in movement disorders. At the level of the striatum, the motor circuit is largely controlled by the putamen (Kunzle 1975), supporting the functional subdivisions of the striatum described earlier. The role of the D2 receptor in motor control is supported by the extrapyramidal side effects of antipsychotic drugs (tremor and bradykinesia), which antagonise D2 receptor sites.

Dopamine and Motor Control in AD

In AD, nigrostriatal dopamine is relatively preserved (Piggott et al., 1999). However, extrapyramidal symptoms (EPS) (bradykinesia and rigidity) are reported to emerge in 35-40% of patients (Murray et al., 1995). Evidence regarding the dopaminergic contribution to such symptoms is unclear, with some studies reporting reduced

markers of nigrostriatal dopamine function post-mortem (Joyce et al., 1998; Murray et al., 1995; Sahlberg et al., 1998) and *in vivo* (Rinne et al., 1998), while others report little or no abnormalities in nigrostriatal dopaminergic function in those with EPS (Piggott et al., 1999; Tyrrell et al., 1990). The latter studies suggest that extranigral factors may be contributing to the bradykinesia and rigidity observed in patients with AD. Only one study to date has directly assessed the role of D2/3 receptors in motor control in AD. This study used PET imaging to demonstrate a significant association between higher striatal D2/3 receptor availability and increased motor speed (Reeves et al., 2010). The association was most marked in the sensorimotor striatum, consistent with the corticostriatal circuitry described in Section 1.2.1, whereby the sensorimotor striatum receives its densest input from motor and premotor cortices (Flaherty & Graybiel 1994).

Figure 1.2: The Direct and Indirect Pathways of Motor Control



Adapted from Belujon & Grace (2011)

1.3.2 Role of Dopamine in Cognitive Control

Overview

Cognitive deficits are frequently reported in a range of neurological disorders in which dopamine has been implicated, including schizophrenia, attention deficit hyperactivity disorder (ADHD), and PD (Nieoullon 2002). Such observations, together with awareness that the basal ganglia project to several non-motor areas, support the role of dopamine in influencing a broad range of behaviours (Alexander et al., 1986). One of the most established findings of the role of dopamine in cognition came from the work of Goldman-Rakic's research group, who reported that specific cortical depletion of dopamine by 6-Hydroxydopamine (6-OHDA) impaired performance on a working memory task in monkeys (Brozoski et al., 1979). In humans, pharmacological agents which reduce dopamine transmission by either antagonising dopamine receptors, or depleting dopamine precursors, such as tyrosine and phenylalanine, have resulted in impaired performance on a range of executive tasks such as working memory, planning, and attentional set shifting (Harmer et al., 2001; Mehta et al., 1999).

In vivo evidence of the role of D2/3 receptors in cognition is provided by PET and single photon emission computerised tomography (SPECT) studies, which report decreased striatal binding to be associated with tasks of working memory and other executive functions (Backman et al., 2000; Lawrence et al., 1998; Reeves et al., 2005; Volkow et al., 1998; Yang et al., 2004). The recent development of higher affinity D2/3 radiotracers such as [¹¹C]FLB-457, has enabled the role of D2/3 receptors outside the striatum to be investigated, and studies have suggested a role of hippocampal D2/3 receptors in memory. Other tasks requiring executive processes were also associated with hippocampal D2/3 receptor availability, a finding which the authors explained by a postulated hippocampal-prefrontal pathway (Takahashi et al., 2007; Takahashi et al., 2008).

Dopamine and Cognitive Control in AD

Few studies have looked directly at the impact of dopaminergic function upon cognition in AD. A single study proposed that hippocampal D2/3 receptors contribute to performance on tasks of memory and naming in AD (Kempainen et

al., 2003). This suggestion was based on two findings: firstly, D2 receptor availability was reduced by 34% and 14% in the right and left hippocampus respectively in AD patients compared to healthy controls; and secondly, the magnitude of binding was positively associated with verbal memory performance and picture naming. Further support for the role of dopamine in cognition is provided by a study which demonstrated that increased striatal dopamine synthesis capacity in AD was associated with higher scores on the MMSE (Itoh et al., 1994). Most recently, the D2/3 radiotracer [¹¹C]raclopride was used to examine the association between striatal D2/3 receptor availability and cognition. This study found higher striatal D2/3 receptor availability to correlate with sustained attentional performance, with the most marked correlation occurring in the associative striatum. This finding is consistent with the corticostriatal neurocircuitry described in Section 1.2.1, whereby the associative striatum receives its densest input from the prefrontal cortex and has a primary role in attention and executive function (Selemon & Goldman-Rakic 1985). The same study also showed a trend-level association between striatal D2/3 receptor availability and verbal episodic memory (Reeves et al., 2010).

1.3.3 Role of Dopamine in Psychosis

Overview

In addition to cognitive and motor control, dopamine has also been strongly implicated in psychosis. Perhaps one of the most widely researched roles of dopamine is in relation to schizophrenia, a disorder with positive symptoms (hallucinations, delusions), negative symptoms, and formal thought disorder. The first direct evidence of a dopaminergic underpinning to schizophrenia came about in the 1970s, following observations of a high correlation between the antipsychotic potency of neuroleptic drugs and their affinity for binding to dopamine receptors (Creese et al., 1976; Seeman et al., 1975). Subsequent studies using neuroimaging techniques provided further evidence of the role of dopamine in psychosis, reporting an increased striatal density of D2 receptors in drug-naïve schizophrenic patients (Wong et al., 1986), and excessive striatal dopamine release in psychotic patients in response to amphetamine challenge (Laruelle et al., 1996). Such studies provided direct evidence that psychotic symptoms were promoted by excessive D2 receptor

stimulation. Contemporary theories of psychosis have integrated the dopamine hypothesis of schizophrenia with data on motivational salience, to suggest that aberrant signalling of salience due to excessive striatal dopamine activity plays a key role in delusion formation (Kapur 2003). The pre-synaptic dopamine system has also been implicated in psychosis. Studies have demonstrated increased striatal dopamine synthesis capacity (Howes et al., 2007), and increased responsivity of presynaptic striatal dopamine neurones to psychostimulant challenge (Breier et al., 1997) in young adults with schizophrenia compared to their healthy counterparts.

Dopamine and Psychosis in AD

Psychotic symptoms are common in AD, with their prevalence increasing from approximately 25% in mild-AD (MMSE score 21-25) to 50% in those with severe cognitive impairment (MMSE score 10 or below) (Ropacki & Jeste 2005). Contemporary theories suggest that disruption of the cholinergic/dopaminergic axis plays a central role in the formation of delusions in AD (Cummings 1992) (discussed in Chapter 3, Section 3.1.2). This theory, reviewed by Reeves et al. (2012), overlaps with that of Kapur et al. (2003), whereby relative hyperdopaminergia leads to misinterpretation of the environment (Kapur 2003). In support of these theories is evidence that cholinergic denervation in rodents increases striatal dopamine release in response to amphetamine challenge, and subsequently results in psychotic-like behaviour (Mattsson et al., 2007; Mattsson et al., 2004). A dopaminergic contribution to psychotic symptoms in AD is supported by *in vitro* research, which suggests a 70% increase in D3 receptor density in AD patients with a history of psychosis, compared to their non-psychotic counterparts (Sweet et al., 2001). The involvement of dopamine receptors in psychosis is also supported by genetic studies, which have shown variations in the genes encoding D1 and D3 receptors to be associated with hallucinations and delusions, respectively, in AD (Holmes et al., 2001). More recently, *in vivo* evidence has emerged showing increased striatal D2/3 receptors in those with delusions in AD, compared to those without delusions (Reeves et al., 2009).

In summary, dopamine has been implicated in motor control, cognition and psychotic symptoms in AD, and this has been recently demonstrated *in vivo* by

Reeves and colleagues (Reeves et al., 2009; Reeves et al., 2010) in a sample of patients with mild to moderate AD. These findings raise questions as to whether cognitive and motor tasks associated with dopaminergic function could perhaps act as markers of psychotic symptoms in AD. However, the small sample size (N = 23; 7 psychotic) in these studies meant that it was not possible to meaningfully compare psychotic and non-psychotic groups in terms of test performance. The present thesis aims to address this question, and will be discussed in further detail in Chapter 3.

1.4 Aims of Thesis: Part 1

Neuropsychological Assessment

- To test the hypothesis that performance on tests with a demonstrated link with dopamine (striatal D2/3 receptor) function will differ in psychotic versus non-psychotic patients with AD, after controlling for differences in age, education and MMSE.

1.5 Treatment of Psychotic Symptoms in AD

1.5.1 Antipsychotic Medication: Mechanism of Action

Antipsychotic medication is prescribed across a range of disorders for the treatment of psychotic symptoms (delusions and hallucinations). The primary mechanism of action of antipsychotic drugs is antagonism at D2/3 receptor sites. However, due to the crucial role of the dopaminergic system in motor control (Section 1.3.1), motor side effects known as extrapyramidal symptoms (EPS) commonly occur, and include bradykinesia, tremor and rigidity. Such side effects are a serious concern when treating psychotic disorders.

1.5.2 Use of PET Imaging to Guide Antipsychotic Prescribing

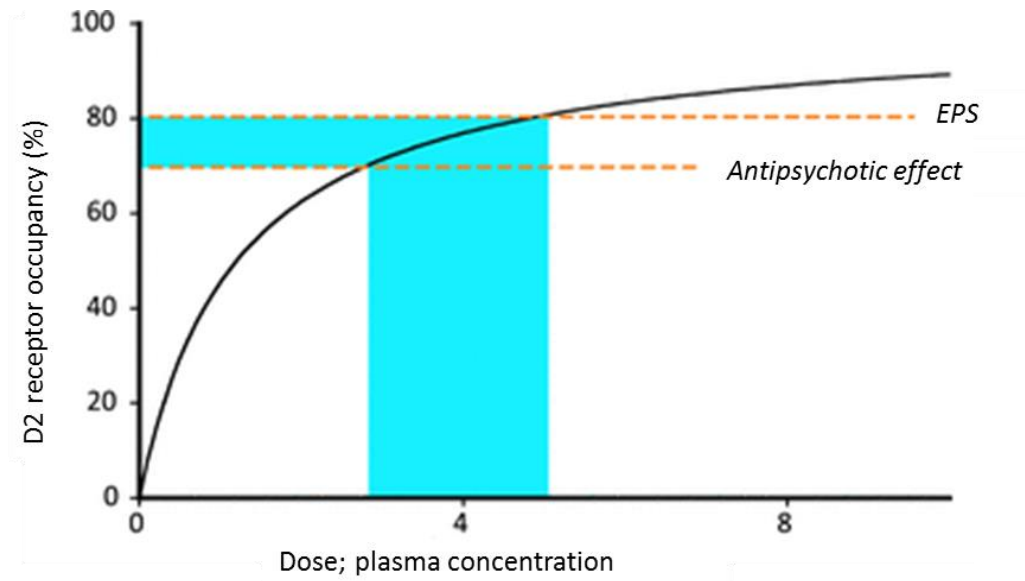
PET imaging has been instrumental in guiding treatment strategies in schizophrenia, through the investigation of the relationship between drug dose, blood levels and central D2/3 occupancy. Studies carried out in the early 1990s established that there is a 'therapeutic window' of D2/3 receptor occupancy, within which symptom reduction is accompanied by minimal EPS. *In vivo* imaging of dopamine D2/3 receptors was first achieved by Wagner and colleagues in 1983 (Wagner et al., 1983). Following this, several studies used PET imaging techniques to study the role of D2 receptors in antipsychotic response, and reported high D2/3 occupancy in patients treated with antipsychotic drugs (Cambon et al., 1987; Farde et al., 1986; Smith et al., 1988). In 1988, Farde et al. reported 65-85% occupancy of D2/3 receptors in patients treated with 11 chemically distinct antipsychotics (Farde et al., 1988). These studies provided direct *in vivo* evidence that antipsychotic effects were mediated by D2/3 receptors. In 1992, Farde et al. was the first to measure the correlation between D2/3 receptor occupancy and the clinical effects of antipsychotic treatment (Farde et al., 1992). In an open study of 22 patients with schizophrenia, the authors observed a uniformly high D2/3 occupancy of 70-89% at conventional doses, and that occupancy was higher in patients exhibiting EPS. These results were supported by Nyberg and colleagues, who reported a threshold for antipsychotic effects at about 70%, and a distinct threshold for EPS at 80%. Based on these findings, the authors postulated a 'therapeutic window' of 70-80% D2/3 occupancy, illustrated in Figure 1.3 (Nyberg et al., 1995). Two double blinded studies supported

the observation of a ‘therapeutic window’, and in particular the threshold of 80% occupancy for EPS. However, both studies suggested a lower threshold of 60-65% for antipsychotic effects (Kapur et al., 2000; Nordström et al., 1993). Taken together, these studies led to the suggestion of a ‘therapeutic window’ of 60-80% D2/3 occupancy in young adults, in order to achieve adequate antipsychotic response with low or minimal side effects (Kapur 1998). A direct application of the above findings is observed in studies which have reduced the recommended daily dosage of antipsychotic drugs, based on D2/3 occupancies falling within the ‘therapeutic window’. For example, D2/3 occupancy data suggest 4mg of risperidone as the optimal starting dose in schizophrenic patients, as opposed to 6mg (previously suggested as the standard dose), which caused unnecessarily high D2/3 occupancy and resulted in EPS (Nyberg et al., 1999). Similarly, 2-3mg of haloperidol is recommended, in contrast to 10-20mg advised in previous studies (Kapur et al., 2000). This imaging paradigm has led to huge clinical advances, not only in terms of guiding treatment strategies of schizophrenia in young adults, but also in the development and evaluation of new antipsychotics (de Greef et al., 2011), the comparison of existing antipsychotics (Kapur et al., 1999), and also in developing clinically comparable animal models for the testing of antipsychotic medication (Kapur et al., 2003). The ‘therapeutic window’ of antipsychotic drug action is now widely accepted and has been the subject of several review articles (de Greef et al., 2011; Nord & Farde 2011; Pani et al., 2007).

More recently, high affinity D2/3 receptor radiotracers such as [¹⁸F]fallypride and [¹¹C]FLB-457 have allowed D2/3 receptor availability to be measured in extrastriatal regions, where receptors are present at a much lower density compared to the striatum. This has enabled the role of extrastriatal D2/3 receptors in antipsychotic treatment response to be investigated. Such studies have shown atypical antipsychotics to have higher occupancies in the temporal cortex compared to the striatum (Bigliani et al., 2000; Pilowsky et al., 1997; Xiberas et al., 2001b). Additional studies have implicated temporal cortical D2/3 receptor occupancy in response but not adverse effect profile (Stone et al., 2009). Exploration of the clinical relevance of extrastriatal D2/3 receptor occupancy by antipsychotic drugs is an on-going focus of research (discussed in Chapter 4).

In contrast to the abundance of data on D2/3 occupancy in young adults, this area has been largely neglected in the older population, including those with AD, who are highly sensitive to antipsychotic side effects and would benefit from the optimisation of antipsychotic dosing regimens.

Figure 1.3: Therapeutic Window of D2/3 Receptor Occupancy for Antipsychotics in Young Adults



(Nord & Farde 2011)

1.5.3 Antipsychotic Sensitivity in AD

Current prescribing of antipsychotics in AD is associated with a range of side effects including: EPS (bradykinesia, tremor), sedation, postural hypotension, falls, cerebrovascular events (stroke, transient ischemic attacks) and increased mortality (Ballard & Howard 2006). In a meta-analysis of placebo controlled trials of atypical antipsychotics (Ballard & Howard 2006), AD patients treated with risperidone were twice as likely to experience EPS compared to those taking placebo, even at low doses of 1-2mg. Use of risperidone was also associated with fever and peripheral oedema, while both risperidone and olanzapine significantly increased drowsiness. Both antipsychotics were also reported to cause a 3 fold increase in serious cardiovascular events compared to placebo. Out of a total of 17 placebo controlled trials, using a range of antipsychotics in elderly patients with AD, 15 studies

demonstrated numerical increases of approximately 1.7 fold for the risk of mortality in the drug treated group, compared to those taking placebo. These studies enrolled over 5000 patients in total and were analysed by several groups (Schneider et al., 2005). Examination of the deaths revealed that the majority were caused by cardiovascular events or infections (mostly pneumonia). These findings led to the FDA issuing a black box warning in 2005 against the use of antipsychotics in AD (Leon et al., 2010). As a result, the majority of antipsychotics are not licensed to treat neuropsychiatric symptoms of dementia. However, despite the risks, many are still prescribed off-label due to the lack of alternative pharmacological treatments for behavioural or psychotic symptoms.

The reasons for the heightened sensitivity to antipsychotic drugs observed in the elderly are poorly understood. Several theories have been proposed (illustrated in Figure 1.4) including: the peripheral pharmacokinetic theory, whereby a higher drug plasma level is reported for a given dose; the central pharmacokinetic theory, which proposes higher D2/3 occupancies for a given dose of drug; and the pharmacodynamic theory, which postulates that an age-related reduction in D2/3 receptor reserve results in a greater functional outcome for a given D2/3 receptor occupancy (Uchida et al., 2009b) (discussed in Chapter 5).

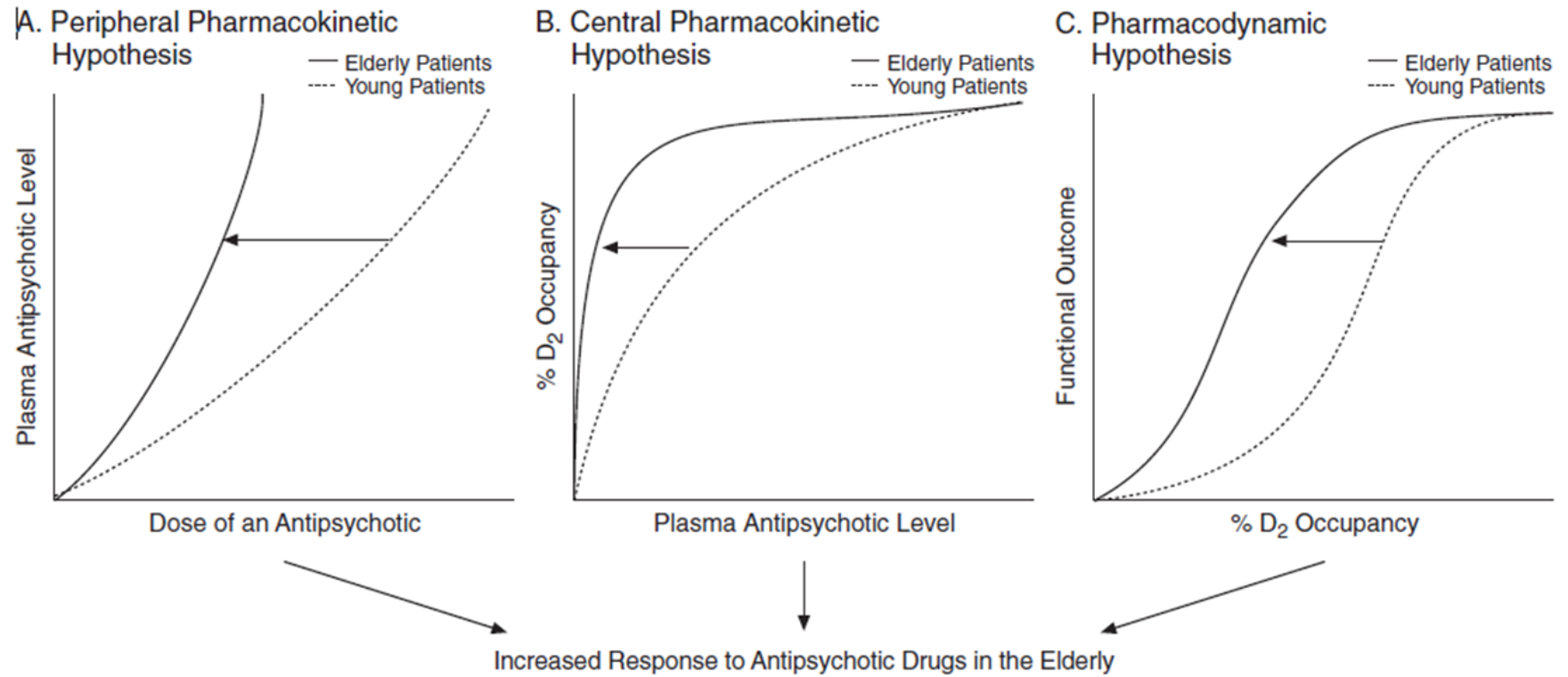
However, no studies have directly assessed the contribution of each of these theories to the heightened antipsychotic sensitivity observed in AD. To date, there have been no studies of D2/3 receptor occupancy in patients with AD, nor any research into the clinical relevance of extrastriatal D2/3 receptors to therapeutic response in this population. There is an urgent clinical need for both lines of research in the AD population, in order to improve efficacy and reduce adverse effects with antipsychotic drugs. One reason for the lack of research in older adults is the fact that many scanning protocols require lengthy periods of time in the scanner, which is particularly difficult for patients with cognitive impairment. Adapting the scanning procedure to reduce the time spent in the scanner could enable the advancement of research in this field. This issue is addressed in further detail in Chapter 4.

1.6 Aims of Thesis: Part 2

PET Imaging

1. To determine the test-retest reliability of regional binding of the PET dopamine D2/3 receptor radiotracer [¹⁸F]fallypride in eight healthy older (>65 years) adults, using a protocol that has been specifically adapted to minimise the amount of time spent in the scanner, thus making it feasible for use in the older population.
2. To further adapt and optimise [¹⁸F]fallypride imaging for use in D2/3 receptor occupancy studies in AD.

Figure 1.4: Mechanisms of Antipsychotic Sensitivity in the Elderly



(Uchida et al., 2009b)

Chapter 2: Overview of Methodology

This chapter provides a general overview of the methodology employed in the present thesis. There are three experimental studies in this thesis, one which evaluates neuropsychological tests and two which involve PET imaging. This chapter has been divided into two parts, in order to deal with the neuropsychology and imaging components separately. Part 1 details the methodology relating to neuropsychological testing and Part 2 details the methodology used for the PET imaging studies. The structure within each part is outlined below.

Part 1: Neuropsychological Testing

- 2.1 Methodology used to establish the neuropsychological profile of psychotic symptoms in AD. This includes study design, subject criteria, informed consent procedure, ethical approval, and sample size considerations.
- 2.2 Rationale provided for the choice of neuropsychological tests and carer-rated measures, and details of how these tests were administered.
- 2.3 Data analysis.

Part 2: PET Imaging

- 2.4 Overview of methodology associated with PET. This includes the principles of PET imaging, PET quantification and choice of radioligand.
- 2.5 Methodology used to establish the test-retest reliability of an adapted [¹⁸F]fallypride PET imaging protocol in older people. This includes study design, subject criteria, informed consent procedure and the scanning protocol.
- 2.6 Methodology used to optimise [¹⁸F]fallypride PET imaging for D2/3 receptor occupancy studies in AD. This includes study design, subject criteria, informed consent procedure, scanning protocols, and a description of the cognitive and motor tests used for baseline and follow up assessments.
- 2.7 General methodology common to both experiments including: ethical approval, sample size and general data analysis.

2.1 Neuropsychological Profile

2.1.1 Summary of Study Design

Subjects with AD (Group 1 with psychotic symptoms, Group 2 without psychotic symptoms) were recruited to the study with the aim of establishing the neuropsychological profile of psychotic symptoms in AD. Subjects completed a neuropsychological test battery over two visits (1 week apart). The test battery included computerised and pen-and-paper measures that assessed performance in different cognitive domains. Carer-rated scales of symptom severity were used to determine the frequency and severity of psychotic symptoms (delusions and hallucinations).

2.1.2 Recruitment and Screening

Inclusion Criteria

Patients were included in the study if they were aged between 65 and 95 years and fulfilled NINCDS-ADRDA criteria for AD (McKhann et al., 1984) (described in Chapter 1, Section 1.1.2).

Exclusion Criteria

Patients were excluded from taking part on the basis of medical, psychiatric and medication history. In terms of medical history, exclusion criteria included a history of epilepsy, substance misuse, traumatic brain injury or addiction (which was confirmed with the referring medical practitioner). The Geriatric Depression Scale-15 (described in Section 2.2.1) was administered with a cut off score of <6 out of 15 to exclude those with depression, which may have affected performance on the test battery. Patients were also excluded on the basis of past or current psychiatric illness (confirmed with the referring medical practitioner). A detailed medication history was taken and patients were excluded if they were prescribed psychotropic medication (including antidepressants and anxiolytics), or other medication that might interfere with dopamine function. A modified version of The Unified Parkinson's Disease Rating Scale (Ballard et al., 1997) (described in Section 2.2.1) was used to screen for the presence of overt motor symptoms (bradykinesia, rigidity, facial masking or tremor). Patients with a score of >8 were excluded, in order to rule

out the potential confounding influence of motor symptoms upon striatal dopaminergic indices, and to avoid the potential for inclusion of patients with Lewy Body Dementia (DLB). Patients with other symptoms suggestive of a possible diagnosis of DLB (frequent falls/syncope, prominent visual hallucinations, or marked fluctuation in cognitive ability) were also excluded. A score of <10 on the MMSE (described in Section 2.2.1) was also a cause for exclusion in order to avoid floor effects on the neuropsychological tests.

Recruitment Procedure

Subjects were recruited from the Institute of Psychiatry Dementia Case Register (n = 3, described in Section 2.5.2), memory clinics (n = 66), and community mental health teams for older adults (n = 11) within the catchment area of the South London and Maudsley NHS Foundation Trust (SLaM). The researcher attended weekly team meetings at the Croydon Memory Service to identify potential candidates for the study. In an attempt to facilitate recruitment further, permission was obtained from Consultant Psychiatrists and keyworkers within each of the teams, to search their caseloads on the Electronic Patient Records System for potential subjects. Once the keyworkers consented to their patients being contacted, the researcher made initial contact with the patients via the telephone. After obtaining verbal consent, a one-page summary leaflet and more detailed information sheet were sent in the post to the patients and their caregivers, respectively. A follow-up phone call was made to the patients to confirm participation and arrange the first visit. This procedure allowed patients to digest the information provided to them before giving informed consent to participate. The summary leaflet and information sheet used for this study are detailed in Appendix 7.1.1. Recruitment took place between January 2011 and November 2012.

Informed Consent Procedure

Written informed consent from each subject was obtained upon recruitment to the study (see Appendix 7.1.1 for the consent form).

2.1.3 Ethical Approval

This study was approved by The Joint South London and Maudsley and Institute of Psychiatry NHS Research Ethics Committee (written approval is listed in Appendix 7.2).

2.1.4 Sample Size Considerations

Sample size was determined using previous data on AD patients, where the standard deviation (SD) of motor speed was 20% and mean motor speed was found to be 11% higher in the psychotic (n = 7) compared to non-psychotic (n = 16) group (Reeves et al., 2010). To detect a between-group difference of 11% in mean motor speed, a sample size of 50 in each group would be required (power = 0.8, alpha = 0.05; independent samples t-test); and a sample size of 35 in each group would allow differences of 13.6% to be detected.

2.2 Neuropsychological Testing

2.2.1 Screening Tools

Delusions and Hallucinations

A modified version of The Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) was used as a screening tool to identify patients with delusions and hallucinations (see Appendix 7.3). The NPI is a caregiver rated scale that evaluates 12 areas of psychopathology in dementia, 10 neuropsychiatric symptoms (delusions, hallucinations, agitation, depression/ dysphoria, anxiety, euphoria/elation, apathy, disinhibition, irritability and aberrant motor behaviour) and two neurovegetative symptoms (sleep and appetite). Caregivers are first asked a screening question to determine whether or not the symptom is present. If the answer to the screening question is yes, the caregiver is asked about the symptom in further detail and asked to rate the frequency and severity with which it occurs. The NPI has been shown to have good validity and reliability (Cummings et al., 1994).

The screening tools below were used in order to control for the confounding effects of global cognitive functioning, intellectual functioning, level of affect, and dopaminergic function, on other neuropsychological test measures.

Brief Cognitive Screening

The Mini-Mental State Exam (MMSE) (Folstein et al., 1975) was used to briefly assess global cognitive functioning. The MMSE consists of five subtests in the domains of orientation, language, memory, attention and praxis. It is scored out of a total of 30 points, higher scores indicating better performance.

Premorbid Intellectual Functioning

The National Adult Reading Test (NART) (Nelson 1982) was used to provide an estimation of premorbid intellectual functioning. The number of NART errors was used to predict Performance Intelligence Quotient scores (Wechsler 1955), based on regression equations presented by Nelson (1982). The test consists of 50 short words of irregular pronunciation (e.g. deny, prelate). Subjects are asked to read each word out aloud, and the total number of pronunciation errors (out of 50) is recorded.

Geriatric Depression Scale-15

The Geriatric Depression Scale-15 (GDS-15) (Yesavage et al., 1982) which is specifically designed for use in the older population, was used as a screening tool for depression. The test consists of 15 ‘yes’ or ‘no’ questions regarding the subject’s mood. The simplicity of the questionnaire enables its use in those with cognitive impairment.

Unified Parkinson’s Disease Rating Scale

The Unified Parkinson’s Disease Rating Scale (UPDRS) (Motor Examination) (Ballard et al., 1997) was used to screen for the presence of parkinsonian symptoms, and hence disruption to the dopaminergic system. The modified version used in the present study focused solely on overt motor symptoms including bradykinesia, rigidity, facial masking, resting tremor, and action or postural tremor. Each symptom was rated on a scale from 0 (no symptom) to 4 (marked symptoms) and added together to give a total score out of 20.

2.2.2 Hypothesis-Driven Tests

Two neuropsychological tests were chosen on the basis of demonstrated links with dopaminergic function, and are described in further detail below.

Rapid Visual Information Processing (RVP)

The RVP task is a test of visual sustained attention and forms part of the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, UK) (Robbins et al., 1994). There is robust evidence to support a role of corticostriatal dopaminergic neurocircuitry in the control of attention maintenance (Grafton et al., 1995; Graybiel 1995; Jueptner et al., 1997a; Jueptner et al., 1997b). The RVP was chosen in preference to other attentional tasks because it has been adapted for use in the AD population (Egerhazi et al., 2007; Jones et al., 1992), and performance accuracy has been shown to correlate negatively with striatal D2/3 receptor availability (Reeves et al., 2010).

During the test, a white box appears in the centre of the computer screen, inside which single digits from two to nine appear in a pseudorandom order at a rate of 100 digits per minute. The original version of the test requires subjects to press a button whenever specific three-digit sequences ('357', '246' or '468') appear on the screen, over a 3 minute test period. In the AD population, the test has been modified such that subjects are required to recognize only one sequence ('357'), thus reducing the working memory component of the task (Jones et al., 1992).

In the present study, the RVP was carried out using a touch screen computer and a button box. Prior to starting the test, subjects were familiarised with the apparatus and asked to practice pressing the button whilst simultaneously looking at the screen. Once this had been mastered, subjects were given a 2 minute 'practice' session, during which the task requirements were made clear. A maximum of two practice runs were allowed before commencing the test, which ran over 3 minutes. Correctly detected sequences ('hits') and false identifications ('misses') were recorded in addition to the response time for each 'hit'. For the purposes of the current analysis, the accuracy of test performance was indexed by the number of hits, with a maximum achievable score of 24 (recorded in three blocks, with eight target sequences in each).

Simple Reaction Time (SRT)

The SRT task is a test of motor speed which forms part of the CANTAB. There is strong evidence to support the role of corticostriatal dopamine function in visuomotor control (Jueptner et al., 1997a). This test was chosen as a more accurate measure of motor speed than the motor screening test (MOT), which was previously found to correlate positively with D2/3 receptor availability (Reeves et al., 2010). During the task, a white box appears in the centre of the computer screen. The subject is asked to press a button as quickly as they can when the white box appears on the screen. In the present study, the SRT was carried out using a touch screen computer and a button box. Prior to starting the test, subjects were familiarised with the apparatus and asked to practice pressing the button whilst simultaneously looking at the screen. Once this had been mastered, subjects were given a ‘practice’ session containing 24 trials, during which the task requirements were made clear. Cues on the screen guided the subject if they were responding too soon or too late to the stimulus. After the practice session there was a pause to ensure the subject understood the instructions and was comfortable using the computer. The pause was followed by two blocks of assessed trials, with a brief pause between the two. Each block contained 50 trials. The average response time over the two assessed trials was recorded.

2.2.3 Neuropsychological Test Battery

Neuropsychological tests were grouped into separate cognitive domains, in order to identify if discrete functional networks are associated with psychotic symptoms in AD. The tests used within each domain are described below, together with their psychometric properties. Many of the tests used are taken from The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) (Morris et al., 1989). This is a global scale of cognition, however the individual subtests are commonly used as standalone measures of specific aspects of cognition, and have demonstrated good inter-rater and test-retest reliability (Morris et al., 1989; Welsh-Bohmer & Mohs 1997). Validity of the tests has also been demonstrated by both cross-sectional and longitudinal studies showing a progressive decline in performance with disease severity (Fillenbaum et al., 2008; Morris et al., 1993).

Memory

Immediate verbal recall: measured using the immediate word list task from the CERAD. Subjects read aloud a list of 10 words, after which they are asked to immediately recall as many words as they can remember. They are shown the word list three times in total. For the purpose of the current study, the total number of words recalled over the three trials was measured.

Delayed verbal recall: measured using the word list recall task from the CERAD. Subjects are asked to recall as many words as they can remember from the above task, after a short delay. During the delay, the subjects are distracted by continuing with other tasks from the CERAD. Performance is measured by the number of words correctly recalled. The total score is measured out of 10.

Delayed verbal recognition: measured using the word list recognition task from the CERAD. After a delay, subjects are shown the words seen earlier, together with 10 new words, and are asked to identify which of the words were shown previously. The number of words correctly identified as previously present or absent is recorded. The total score is measured out of 20.

Delayed visual recall: measured with the constructional praxis recall task from the CERAD. After a delay, subjects are required to recall shapes copied earlier in the assessment procedure. The accuracy of the drawings is scored out of a total of 11 points.

Delayed visual recognition: measured using the Camden Short Recognition Memory Test for Faces (Warrington 1996). Subjects are shown 25 different faces, and asked to judge whether each face is 'pleasant' or 'unpleasant'. They are then shown two faces per page and asked to identify which they have seen previously. Performance is measured by the number of faces correctly identified. This test was developed to provide a short and quick recognition memory test. Validation studies have been performed and the discriminative power of the test has been established by assessing patients with dementing illnesses (Warrington 1996).

Executive Function

Digit Span: taken from the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler & Corporation 1997). Subjects are asked to repeat a string of digits either forwards or in reverse order, ranging from two to nine numbers. Performance is measured by the total number of sequences correctly repeated. High test-retest reliability has been reported for the digit span test (Iverson 2001). The validity of WAIS-III has been demonstrated by high correlations with its predecessor, the WAIS-R, and other tests of intellectual function including the Dementia Rating Scale (Strauss et al., 2006).

Semantic and Phonemic Fluency (Benton 1976): subjects are given 1 minute to retrieve as many words as possible that start with a specific letter (C, F, L: Phonemic Fluency), or belong to a certain semantic category (animals, fruits, vegetables: Semantic Fluency). The total number of words is used as the outcome measure. Verbal fluency tasks have high test-retest reliability (0.79 and 0.80 for Semantic and Phonemic Fluency respectively), and validity is demonstrated by the sensitivity of the tasks to distinguish between patients with frontal lesions and healthy controls (Homack et al., 2005).

Motor Inhibition: measured using the Go/No-Go task (Rubia et al., 2001). This task measures the ability to inhibit a motor response and selective attention. A motor response has to be selectively executed or inhibited depending on whether a 'go' or 'no-go' stimulus appears on a computer screen. This particular version of the task was originally designed for use in children with ADHD. The 'go' stimulus, an image of an aeroplane, appeared 77.4% of the time, and the 'no-go' stimulus, an image of a green 'enemy planet' appeared in 22.6% of trials. The task was administered twice, once with each hand, to assess for laterality effects. Each round of the task consisted of 150 trials, with the first five serving as a practice run. The interstimulus interval (ISI) was 1 second. Instructions were to respond as fast as possible to the 'go' stimulus (aeroplanes), but not to respond to the 'no-go' stimulus (enemy planets). The validity of this version of the Go/No-Go task to measure impulsivity is demonstrated by the impaired performance of children with a specific phenotype of ADHD, compared to psychiatric, and healthy, controls (Rubia et al., 2001).

Verbal Inhibition: measured using the Hayling Sentence Completion task (Burgess et al., 1997). This task measures response initiation and response suppression, and involves inhibiting prepotent responses. The researcher reads aloud a list of sentences which have the last word missing. Subjects must complete each sentence with a relevant word in part 1. In part 2, the word used to complete the sentence must have no association to the sentence. The outcome measures in the current study included total time to respond in part 2 ('Hayling inhibition time'), and total number of errors made. The test-retest reliability for the 'Hayling inhibition time' score is adequate (0.78), however a lower reliability is reported for the total number of errors (0.52) (Burgess et al., 1997). The validity of the test has been demonstrated by reports of impaired performance in those with frontal lobe lesions (Burgess et al., 1997) and in a variety of conditions in which executive dysfunction has been implicated, including AD (Collette et al., 2002; Salmon et al., 2000).

Language

Boston Naming Task: taken from the CERAD. Subjects are asked to name 15 pictures ranging from high frequency objects (e.g. house, bed), to low frequency objects (e.g. hammock, sugar tongs). Performance is measured by the total number of correctly named pictures.

Praxis

The Clock Drawing Task (Shulman et al., 1986): subjects are presented with a large printed circle and asked to draw the numbers in the circle so as to resemble a clock face. They are then asked to set the hands on the clock to 'ten past eleven'. Performance is scored on a scale of 1-6 using the Schulman scoring system, whereby a score of 1 is given to a drawing with perfect resemblance to a clock, and a score of 6 when the drawing has no representation of a clock. The Shulman scoring system shows good inter-rater and test-retest reliability, a high correlation with other cognitive measures e.g. MMSE, and good concurrent and predictive validity for detecting cognitive change (Shulman 2000).

Constructional Praxis: measured using a task from the CERAD, which involves subjects copying four pictures of increasing complexity. Accuracy of drawings is scored out of a total of 11.

Visuoperceptual Function

The Visual Object and Space Perception Battery (VOSP) (Warrington & James 1991): the VOSP consists of eight individual subtests, however only four were used in the current study. Descriptions of the tasks are as follows, the first two measuring object perception and latter two measuring space perception: (i) Incomplete Letters - subjects are asked to identify 20 letters which are 70% obliterated; (ii) Object Decision - subjects are presented with 20 arrays, each of which displays 2D silhouettes of one real object and three distractors, and are asked to point to the real object; (iii) Number Location - subjects are asked to identify the number corresponding to the position of a dot; (iv) Cube Analysis - subjects are asked to count the number of solid bricks illustrated. Each of the subtests have been well validated, through studies demonstrating the ability of the tasks to distinguish between patients with right and left hemisphere lesions and medical controls (Warrington & James 1991). Data on the reliability of the tests is limited however, with one study reporting specificities ranging from 71.2% (Number Location) to 98.2% (Incomplete Letters), and test-retest reliabilities ranging from 0.54 (Incomplete Letters) to 0.84 (Number Location) (Bonello et al., 1997).

2.2.4 Procedure for Administration of Neuropsychological Tests

Subjects completed a neuropsychological test battery over two visits, in order to avoid fatigue effects. The visits were separated by approximately 1 week. During the first visit, subjects completed all screening measures, tasks from the CERAD, the Digit Span Test and the computerised SRT and RVP tasks. The NPI was also administered to the informants on this visit. During the second visit, the remaining tests were completed. This order of test administration was chosen to ensure the two visits were balanced in terms of duration and complexity of tasks.

2.3 Statistics

All statistical analyses were carried out using SPSS 19 (www.spss.com). Between-group differences in demographic data were analysed using independent samples t-tests, with the presence of psychotic symptoms as the grouping variable. Separate MANCOVAs (multivariate analysis of covariance) were performed for multiple dependent variables in specific cognitive domains, and ANCOVAs (analysis of covariance) were carried out where there was only one dependent variable in a cognitive domain. Age, MMSE score and years of education were controlled for in each analysis (unless otherwise stated). Further detail of the analysis procedure is provided in Chapter 3, Section 3.2.4.

2.4 Part 2: PET Imaging

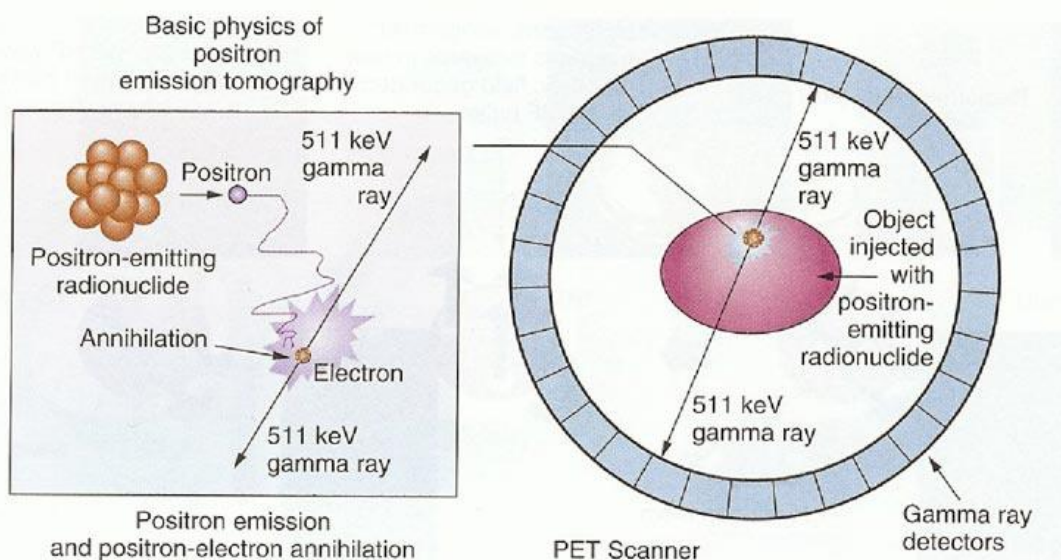
2.4.1 Basic Principles of PET Imaging

PET is a non-invasive imaging technique which measures the spatial and temporal distribution of radiotracers labelled with positron emitters in the body or brain of human subjects. There are several steps involved in a typical PET scan. Firstly, positron emitting radionucleotides are produced by nuclear reactions using charged particle beams. This takes place in a cyclotron. The radionucleotides are then chemically incorporated into receptor specific ligands. The radiotracer (ligand and radioactive isotope) is then intravenously injected into the peripheral circulation of the patient, who is located within the bore of the PET scanner. The tracer will then accumulate in regions where the specified receptor is present. Once injected, the unstable radionucleotides undergo positron decay, whereby a nucleus with too low a neutron-to-proton ratio converts a proton (p) to a neutron (n), emitting a positron (e^+) and a neutrino (ν) which carries off excess energy. This is described by the equation: $p = n + e^+ + \nu$. The emitted positron will travel a short distance before it collides with an electron. Both positron and electron annihilate creating two 511 KeV gamma rays. The gamma ray photons are emitted 180° apart from one another and are detected by scintillation crystals in the scanner, creating a burst of light inside the crystal. The scintillators are coupled to photomultiplier tubes, which convert the light photons to a measurable electrical pulse, which is then sent to a computer. The two gamma-rays must be detected simultaneously, or within a very narrow time window

(a few nanoseconds) in order for this technique to work. The source of the photons is then able to be localised along a straight line (coincident line), due to the gamma photons being emitted at 180° to one another. Data of thousands of coincident lines are collected at different angles and different time points, and can be reconstructed to form an image of the distribution of radioactivity in a subject's brain. For the purpose of the current thesis, the regional levels of radioactivity are assumed to indicate available receptor density. The process described above is illustrated in Figure 2.1.

When gamma rays are given off from a person, scatter occurs within the brain and their progress is impeded ('attenuated') by skull, tissue and other brain structures. In order to correct for this in each individual, a CT scan (taken over 30 seconds) is carried out prior to the main (dynamic) scan, to measure individual attenuation. With attenuation correction and scatter correction calculated for the individual, a PET scanner is thus able to produce quantitative images, in that the activity per pixel can be measured in absolute terms, Becquerel (Bq) per pixel (Paans et al., 2002). The spatial resolution achievable on a standard scanner reflects the finite range of the emitted positron and the technical limitations of the scanner.

Figure 2.1: Principles of PET Imaging



(www.cellsighttech.com/technology/pet.html)

2.4.2 Neuroreceptor Quantification

PET techniques allow the quantification of critical components of neurotransmission through the use of radiotracers that target specific (most commonly receptor) sites on pre- or post-synaptic neurones. The total measured activity recorded by the scanner reflects specifically bound, non-specifically bound and unbound (free) radiotracer (Slifstein & Laruelle 2001) in the tissue, plus a small contribution from activity in the blood in the capillaries (typically 5% in the brain). Several factors influence the profile of this activity, including peripheral clearance, regional cerebral blood flow and blood brain barrier (BBB) transport. In order to control for the extraneous factors and relate the measured activity to receptor density, mathematical modelling of the PET data is required. A variety of modelling approaches exist to quantify receptor binding with radioligand imaging, with the choice of model depending on various factors, such as characteristics of the ligand and infusion techniques. However, despite their differences, all models rely on the use of equations with rate constants to determine the movement of the radioligand through the body. By fitting the model to the PET data obtained, the rate constants can be derived, resulting in a quantitative outcome measure, for example the Binding Potential (BP).

BP is the most common outcome measure in neuroreceptor imaging. It is essentially a measure of the available receptor density and the affinity of the ligand for the receptor. The simplest form of deriving BP is explained by *in vitro* radioligand binding assays, from which tracer kinetic models used in PET studies originated.

2.4.3 Compartmental Models

Compartmental models describe the transfer or exchange of radiotracer between different compartments, via first order kinetics or rate constants. The rate constants determine the fractional rate of change of tracer concentration between compartments over time (Lammertsma & Hume 1996).

Radioligand Binding Assays

A two compartmental model is used for radioligand binding assays. Homogenous tissue, together with the radioligand is incubated in buffer solution. The first compartment includes the buffer solution, and the second compartment reflects

receptor rich tissue. A radioligand enters the model in the buffer solution and can then transfer directly into the second compartment by binding to receptors. Association and dissociation to the receptor are measured by the rate constants k_{on} and k_{off} respectively. Over time, the reversibly binding radioligand reaches equilibrium concentrations in buffer solution and tissue. At equilibrium, the rate constants can be simplified to form an 'equilibrium dissociation constant', K_d (k_{off}/k_{on}). The total number of receptors is referred to as B_{max} , and so BP is derived by determining the ratio of bound radioligand concentration to free radioligand concentration at equilibrium (B_{max}/K_d) (Ichise et al., 2001). *In vivo* tracer kinetic modelling is more complex, but is nevertheless based on the same underlying principles.

PET Studies

In vivo PET studies differ from *in vitro* binding assays because of additional factors affecting the flow of the radiotracers, i.e. blood flow, radioligand clearance from plasma, and number and affinity of available receptors (Ichise et al., 2001). PET imaging studies primarily use a three compartmental model (Figure 2.2). The three compartments include the arterial blood or plasma, the free compartment and a specifically bound ligand compartment. A fourth compartment, containing non-specifically bound ligand also exists, and exchanges with the free compartment. However, for most radioligands, the exchange between these two compartments is in rapid equilibrium, and so the free and non-specifically bound compartments are treated as one (referred to as the non-displaceable compartment). This reduces the number of estimated parameters in the model. The specifically bound ligand compartment consists of high-affinity receptors. The transfer rate of radiotracer across the BBB into the non-displaceable compartment is determined by rate constants K_1 and k_2 . The movement of radiotracer between the non-displaceable and specific binding compartments is measured by k_3 and k_4 , which reflects the movement of the radioligand on and off the receptor, respectively (Mintun et al., 1984).

Figure 2.2: The Three Compartment Model



Adapted from Ichise et al. (2001)

Measuring the ratio of the rate constants in the compartmental model can achieve the BP outcome measure. However, several variations have been used in recent years in an attempt to reflect the true *in vitro* B_{\max}/K_d measurement. The discrepancy in deriving BP outcomes is due to different reference concentrations being used to measure the non-specific/free binding. Innis et al. (2007) has produced a consensus nomenclature in order to differentiate between BP values derived from different reference concentrations. BP is described as the ratio at equilibrium of specifically bound radioligand to that of free radioligand in tissue (BP_F), total parent radioligand in plasma (BP_P) and non-displaceable radioligand in tissue (BP_{ND}). The first two require arterial blood sampling, and the latter uses a reference region approach to estimate the non-specific binding. The current thesis uses a reference tissue approach (described below) and will therefore use BP_{ND} as the outcome measure (Innis et al., 2007).

Assumptions of Compartmental Analysis

Compartmental analysis relies on several assumptions in order to reduce the number of estimated parameters and to produce as close an estimate as possible to the true *in vitro* BP. Primary assumptions include the following: the radioligand comes from a single source i.e. arterial blood plasma; there is free movement of the radioligand between arterial plasma and the free compartment; first order kinetics can describe the exchange of radioligand between compartments; non-specifically bound radioactivity in the second compartment equilibrates with free tissue radioactivity, allowing the free and non-specific binding compartments to be merged; and that the kinetic parameters are constant during the study (Ichise et al., 2001).

Reference Tissue Model

As mentioned above, movement of a radiotracer through the body or brain is affected by cerebral blood flow and peripheral clearance. Since the concentration of free radiotracer in the brain cannot be measured directly, arterial blood sampling is used to provide a tracer input function (concentration for 'arterial blood' compartment in Figure 2.2), a metabolite-corrected measurement of the free concentration of the radiotracer in the plasma. This involves arterial cannulation and technical demands.

In order to avoid the invasive procedure involved in arterial blood sampling, alternative methods have been devised which rely on the presence of a reference tissue, which is devoid of the specific binding site. The time course of radioligand uptake in the region of interest is measured against the rate of uptake in a specified reference region. This is known as the reference tissue model (Hume et al., 1992; Lammertsma & Hume 1996). The reference region is assumed to reflect the 'non-displaceable' compartment in Figure 2.2, where no specific binding occurs.

The advantages of the reference tissue approach include less complicated scanning protocols and data analysis procedures, and the fact that no arterial cannulation is needed. It also removes the labour-intensive task of correcting samples for metabolites.

As with most mathematical models there are several assumptions. For example, the level of free and non-specific binding is assumed to be the same in the target and reference region, and it is assumed that the reference region is not affected by the pathology under study (Lammertsma & Hume 1996). The reference region must be chosen carefully, as specific binding in the reference region will underestimate BP (Gunn et al., 1997).

Simplified Reference Tissue Model

In an attempt to improve the reference tissue model, a simplified model was devised, which reduced the large standard errors associated with the parameters in the previous method, and increased convergence rates. The simplified reference tissue model has been shown to yield BP values which are highly correlated to those of the original reference tissue model (Lammertsma & Hume 1996), and will be used for the current study.

2.4.4 Radioligand Selection: [¹⁸F]fallypride

The receptor of interest in the current thesis is the D2 dopamine receptor. However, as mentioned in Chapter 1, the 75% homology of D2 and D3 receptor domains makes it difficult for D2 selective tracers to differentiate between the two receptors (Missale et al., 1998). The remainder of the thesis will thus refer to the target receptors as D2/3. There are numerous radioligands which target D2/3 receptors, including: [¹¹C]raclopride, [¹²³I]IBZM, [¹¹C]FLB-475 and [¹⁸F]fallypride. Of these, only the latter two have a sufficiently high affinity to measure extrastriatal D2/3 receptors, which exist at a density 10-100 fold lower than in the striatum (Kessler et al., 1993). In order to meet the aims of this study, to devise a suitable scanning protocol for imaging D2/3 receptor occupancy in response to antipsychotic treatment in older adults, it is important that we are able to image extrastriatal D2 receptors, given their proposed involvement in antipsychotic treatment response in young adults with schizophrenia (Bigliani et al., 2000; Stone et al., 2009; Xiberas et al., 2001a; Xiberas et al., 2001b).

[¹⁸F]fallypride has been selected for use in the present thesis due to its unique ability to image both striatal and extrastriatal regions in a single scan (Mukherjee et al., 2002). In contrast to the short half-life of carbon 11 (20 minutes) used in the high affinity tracer [¹¹C]FLB-457 (Olsson & Farde 2001), fluorine-18 has a much longer half-life (110 minutes), which enables tracer uptake to achieve a plateau in the striatum, where D2/3 receptor density is greatest (Bouthenet et al., 1991). The use of [¹⁸F]fallypride in the quantification of striatal and extrastriatal D2/3 receptors has been well validated by test-retest studies (Cropley et al., 2008; Mukherjee et al., 2002; Siessmeier et al., 2005), and is a well-established tool for measuring D2/3 receptor occupancy (Kegeles et al., 2008; Kessler et al., 2005; Kessler et al., 2006; Riccardi et al., 2008).

2.5 Methodology for Chapter 4: Establishing the Test-Retest Reliability of an Adapted [¹⁸F]fallypride Imaging Protocol for Use in Older People

2.5.1 Summary of Study Design

A two-scan approach was used to test the reliability of an adapted scanning protocol, used to measure striatal and extrastriatal dopamine D2/3 receptor availability. Subjects were scanned twice at rest, 4-6 weeks apart. The adapted protocol aimed to minimise the time spent in the scanner. It consisted of three scanning sessions, each lasting 30 minutes, over a total duration of 4 hours.

2.5.2 Recruitment and Screening

Inclusion Criteria

Eight healthy volunteers were recruited to the study. Participants were included in the study if they were aged between 65 and 90 years. Eligibility for the study was assessed by a clinician conducting a brief screening of the individual's medical history and current medications. The MMSE and GDS-15 (described in Section 2.2.1) were used as screening tools for this study. Participants had to score >26 out of 30 on the MMSE to rule out a diagnosis of dementia (Folstein et al., 2001), and <6 out of 15 on the GDS-15 to rule out a clinical diagnosis of depression.

Exclusion Criteria

Participants were excluded from taking part on the basis of medical, psychiatric and medication history. In terms of medical history, exclusion criteria included a history of epilepsy, substance misuse, traumatic brain injury, addiction and neurodegenerative disease. Additional exclusion criteria included the presence of conditions that might affect a person's ability to tolerate a brain scan such as significant respiratory or cardiac disease, or severe kyphosis. Participants were also excluded on the basis of past or current psychiatric illness or needle phobia (the latter because the scan required intravenous cannulation). Structural imaging (T1-weighted MRI) was carried out at the Centre for Neuroimaging Sciences to exclude intracranial abnormalities.

Recruitment Procedure

Participants were recruited from the Institute of Psychiatry Dementia Case Register. This database holds information on healthy and cognitively impaired adults interested in research. It was set up within the NHS trust using a grant from the National Institute of Health Research. All subjects on the Register have given consent to being approached about on-going research projects. Access of researchers to the Register is carefully monitored by a manager and a core team of three people, who ensure that potential subjects are not involved in more than one project at a time. Subjects are contacted following their participation in individual projects to ascertain whether they would be willing to be contacted again. In order to facilitate the recruitment procedure, a one-page summary leaflet was distributed to the Case Register team, in order to provide potential volunteers with basic information. If permission was given, contact was then made by the researcher via telephone, and a more detailed information sheet was provided (see Appendix 7.1.2). Recruitment took place between December 2010 and June 2011.

Informed Consent Procedure

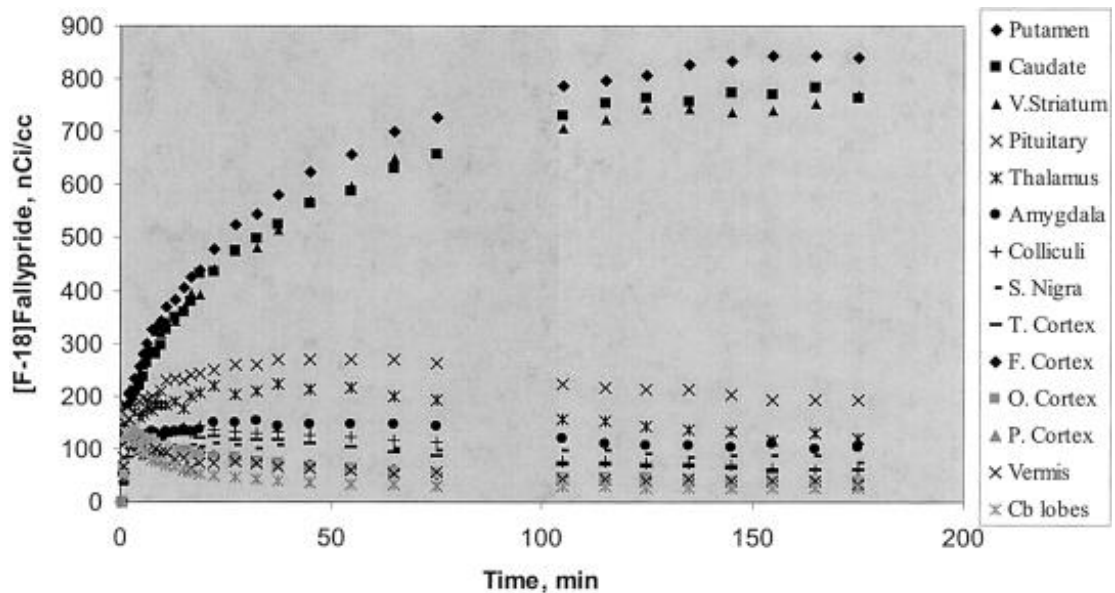
Written informed consent from the subjects was obtained upon recruitment to the study. The information sheets and consent forms used to obtain agreement for the current study are included in Appendix 7.1.2.

2.5.3 Scanning Protocol

The scanning times post injection were: 0-30 minutes, to provide an input function to model a reference region approach; 60-90 minutes, to measure the peak tracer binding within extrastriatal regions; and 210-240 minutes, to ensure that tracer binding achieves a plateau in the striatum of all subjects. These optimal time frames were determined using data from a previous pilot study (Dunn, 2008-preliminary data), and data from receptor occupancy studies using [^{18}F]fallypride in young adults (Kegeles et al., 2008; Kessler et al., 2006). There have been studies which have used protocols requiring a shorter total scanning time, for example 120 minutes (Mukherjee et al., 2002) and 180 minutes (Vernaleken et al., 2011), however the time-activity curve from the former study shows uptake in the striatum to still be

climbing towards a plateau at the end of the final scanning session (see Figure 2.3), and the latter study reported that tracer may take up to 210 minutes to achieve equilibrium in a small proportion of people. Therefore, the total scan duration of 240 minutes was chosen in the current study to ensure tracer uptake in the striatum had reached equilibrium. The time frames of the adapted protocol allow investigation into the effect of shorter scan durations without reducing the total uptake time, which could lead to inaccuracies in the quantification of striatal BP_{ND} .

Figure 2.3: Regional Time-Activity Curve of [^{18}F]fallypride Uptake Over 180 minute Scanning Session



(Mukherjee et al., 2002)

2.5.4 Statistics

A paired t-test was used to compare the administered dose of [^{18}F]fallypride between test and retest scans. BP_{ND} values for test and retest scans were determined, and the absolute variability of test-retest reproducibility was calculated. The intraclass correlation coefficient (ICC) (Fisher 1958) was also calculated to measure the reliability of the test-retest BP_{ND} values for each region of interest. Further details of the statistical analysis are provided in Chapter 4, Section 4.2.4.

2.6 Methodology for Chapter 5: Optimising [¹⁸F]fallypride Imaging for D2/3 Receptor Occupancy Studies in AD

2.6.1 Summary of Study Design

A two-scan approach was used to test the feasibility of an adapted scanning protocol used to measure striatal and extrastriatal D2/3 receptor availability. Subjects were scanned twice, at rest, using interrupted scanning protocols designed to reduce the time spent in the scanner. The first (baseline) scan was carried out prior to commencing amisulpride treatment and was used to provide a baseline for comparison with post-treatment scans. The second scan took place after 2-8 weeks of amisulpride treatment (50-200mg daily), when a therapeutic response (symptom reduction of >25%) had been achieved. The protocol consisted of two scans of 20 minutes and one scan of 40 minutes, over a total duration of 2.5 hours.

Neuropsychiatric symptoms were assessed prior to baseline and post-treatment scans using the NPI, and motor side effects were measured with the Simpson-Angus Scale (SAS) (Simpson & Angus 1970) (both assessments are detailed further in Section 2.6.5). Other side effects, including falls and sedation, were also recorded.

2.6.2 Recruitment and Screening

Inclusion Criteria

Patients were included in the study if they were aged between 65 and 90 years, fulfilled the NINCDS-ADRDA criteria for AD (McKhann et al., 1984) (described in Chapter 1, Section 1.1.2), and were eligible to receive amisulpride treatment for behavioural or psychotic symptoms, but had not yet commenced medication. Clinical assessment included the MMSE (described in Section 2.2.1) to determine the severity of dementia (27 = normal, 21-26 = mild, 11-20 = moderate, <10 = severe) (Folstein et al., 2001).

Exclusion Criteria

Exclusion criteria are similar to those described for healthy control subjects in Section 2.5.2. In addition, a detailed medication history was taken and patients were excluded if they were prescribed psychotropic medication that might interfere with dopamine function. A modified version of the UPDRS was used to screen for the

presence of overt motor symptoms (bradykinesia, rigidity, facial masking or tremor). Patients with a score of >8 were excluded in order to rule out the potential for inclusion of patients with DLB. Patients with other symptoms suggestive of a possible diagnosis of DLB (frequent falls/syncope, prominent visual hallucinations, or marked fluctuation in cognitive ability) were also excluded.

Recruitment Procedure

Subjects were recruited from inpatient units (n = 2) and community mental health teams for older adults (n = 6) within the catchment area of the South London and Maudsley NHS Foundation Trust (SLaM). Researchers established links with Consultants and keyworkers working within the teams, who were then responsible for identifying and referring patients who might be suitable to take part in the study. In order to facilitate this, a one-page summary leaflet was distributed to each team to provide potential volunteers with basic information. If permission was given, contact was then made by the researcher via telephone, and a more detailed information sheet was provided (the leaflet and information sheet used for this study are detailed in Appendix 7.1.3). Recruitment took place between April 2012 and January 2013.

Informed Consent Procedure

Initially, written informed consent was required from all subjects. However, given the fact that antipsychotics were being prescribed most commonly in people with moderate to severe AD, the ethics committee approved a substantial amendment request which enabled consent to be obtained from the carer on the patients behalf (see Appendix 7.2.1). Subsequently, verbal and written informed consent was obtained from subjects who were able to give fully informed consent (n = 3), or from the carer, who acted in the capacity of a personal legal representative and gave consent on his/her behalf (n = 5). The consent form used in the current study is detailed in Appendix 7.1.3.

2.6.3 Scanning Protocol

The baseline scanning protocol is identical to that used in the reliability study, detailed in Section 2.5.3. The original scanning protocol for the post-treatment scan

consisted of two scanning sessions at 0-60 minutes and 110-150 minutes post-injection. However, a substantial amendment was made to the protocol in order to further reduce the first 60 minute scanning session (see Appendix 7.2.2). The reason for this amendment was to improve the tolerability of the scanning protocol in subjects who were physically frail and/or more severely cognitively impaired than was anticipated when the study was originally designed. The amended scanning times post-injection were as follows: 0-20 minutes, to provide an input function to model a reference region approach; 40-60 minutes, to measure peak tracer binding within extrastriatal regions; and 110-150 minutes, to measure peak tracer binding within the striatum. The total scanning time for the post-treatment scan is shorter than the baseline scan due to a reduced number of D2/3 receptor sites available for tracer binding following antipsychotic medication. Therefore, [¹⁸F]fallypride uptake achieves an earlier plateau. Optimal time frames for the post-treatment scan were derived from previous occupancy studies using [¹⁸F]fallypride in young adults, which show tracer uptake to plateau between 2-3 hours (Kegeles et al., 2008; Kessler et al., 2006).

2.6.4 Amisulpride Dose-Titration

After the baseline scan, amisulpride was commenced at a starter dose of 25mg or 50mg, depending on the preference of the prescribing clinician. Follow-up assessments were carried out every 14±7 days, with the aim of assessing symptom and side effect profile through amisulpride dose titration up to a maximum of 200mg daily. This dose range was based on data from open-label trials in elderly patients with AD (Lim et al., 2006; Mauri et al., 2006). One study began prescribing at 50mg/day, and titrated upwards to a maximum dose of 400mg/day. The mean dose prescribed was 85±53.3mg/day, which resulted in >50% reduction in NPI scores in 80% of subjects. Of those that developed EPS, 67% were taking >100mg/day of amisulpride. However, another study showed doses up to 200mg/day were tolerated by patients with moderate-severe AD, and resulted in a significant decrease in NPI score in all patients, with no significant motor effects. Data from the two studies together support a dose range of 50-200mg daily of amisulpride.

In our sample, medication was administered in the evening by a carer in all but one subject, who lived alone and in whom compliance was facilitated through the use of a blister pack. Subjects were scanned when a reduction in total symptom ratings (summed total of delusions, agitation and hallucinations domains) of 25% or more had been achieved.

Amisulpride was chosen because of its favourable side effect profile compared to other atypical drugs, including a reduced sedative effect, lower risk of weight gain and metabolic disturbance, and no reports of excess cerebrovascular mortality (Coulouvrat & Dondey-Nouvel 1999). In addition, amisulpride selectively targets D2/3 receptors, which allows investigation into the ‘therapeutic window’ of D2/3 receptor occupancy, one of the main objectives of the current thesis (Cougell et al., 1997). The low affinity of amisulpride for plasma proteins, and the fact that it undergoes primarily renal excretion (hepatic metabolism is negligible) reduces the potential for drug interactions, making it suitable for use in elderly patients who do not have significant renal impairment (Rosenzweig et al., 2002). Furthermore, amisulpride was commonly prescribed within the Trust for the treatment of behavioural and psychotic symptoms in dementia at the time the study was designed, which meant that participation in the study would not be at odds with the standard approach used by prescribers.

2.6.5 Monitoring Neuropsychiatric Symptoms and Motor Side Effects

Neuropsychiatric Inventory

For the purposes of this study, three specific symptom domains from the NPI (described in Section 2.2.1) were assessed - delusions, hallucinations and agitation – with the aim of specifically focusing on symptoms which necessitate the use of antipsychotic medication. Live-in caregivers were asked about symptoms over the preceding month, both at baseline and prior to the post-treatment scan. For each domain, carers were asked a screening question to determine whether or not the symptom was present. If the answer was negative a rating of 0 was given, and if positive, carers were then asked to rate the frequency (1-4) and severity (1-3) of the symptom. The frequency and severity scores were multiplied to give a score from 0 (symptom absent) to 12 (symptom continuously present and a major source of

disruption) for each symptom. The NPI is the standard measure used to assess global psychopathology in clinical trials (Birks 2006).

Simpson Angus Scale

The Simpson-Angus Scale (SAS) (Simpson & Angus 1970) was used to monitor clinically significant motor side effects. The scale includes 10 items: one which measures gait (hypokinesia), six which measure rigidity (arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, and head dropping), and three others measuring glabella tap, tremor and salivation. Each item is rated on a 5-point scale, with a score of 0 meaning the complete absence of the condition, and 4 indicating an extreme form of the symptom is present. The total score of the scale is obtained by adding the items together and dividing by 10. Final scores of up to 0.3 are considered within the normal range. The Simpson-Angus Scale has been shown to have good validity and reliability (Simpson & Angus 1970), and is the most commonly used rating scale for assessing drug induced parkinsonism (Knol et al., 2010).

2.6.6 Statistics

Regional [¹⁸F]fallypride BP_{ND} values were determined for pre- and post-treatment scans and used to calculate D2/3 receptor occupancy. Further details of the statistical analysis are provided in Chapter 5, Section 5.2.6.

2.7 Methodology Common to Chapters 4 and 5

2.7.1 Ethical Approval

Both the reliability and feasibility components of this study were approved by The Joint South London and Maudsley, and Institute of Psychiatry NHS Research Ethics Committee (see Appendix 7.2). Permission to administer [¹⁸F]fallypride was given by the Administration of Radioactive Substances Advisory Committee (ARSAC).

2.7.2 Sample Size Considerations

A sample size of eight was needed for both the reliability and the feasibility study. The sample size is comparable to a previous reliability study of [^{18}F]fallypride, carried out in healthy young adults ($N = 6$) (Mukherjee et al., 2002), and is a standard sample size used to establish the test-retest error of PET radiotracers.

2.7.3 PET Protocol

Subjects were scanned twice at rest on a GE VCT Discovery PET-CT camera (FWHM 5mm), at St Thomas' PET Centre. A moulded head rest and straps were used to minimise head movement and an external webcam was used to detect significant head movements that could degrade the quality of image data. [^{18}F]fallypride was administered via a single bolus intravenous injection of 250MBq. Each scanning session consisted of three dynamic scans in 3D mode, each preceded by a low dose CT scan for attenuation correction. Details of the different scanning protocols are discussed in the relevant results chapter.

2.7.4 General Data Analysis

Data were analysed using a simplified reference tissue model (Lammertsma & Hume 1996), with the cerebellum (excluding the vermis) as a reference region. This method has been validated by a previous study using [^{18}F]fallypride, which reported a significant correlation of BP values derived from quantification models requiring arterial blood sampling and those using the cerebellar reference region approach (Siessmeier et al., 2005). Furthermore, the reference region approach has been used in previous test-retest publications using [^{18}F]fallypride (Cropley et al., 2008; Mukherjee et al., 2002).

Pre-processing

Statistical Parametric Mapping, SPM 8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used for pre-processing, and all other analyses were performed using Matlab (www.mathworks.com). Non-attenuation corrected (NAC), fully 3D iteratively reconstructed PET scans (GE 'VuePoint' reconstruction algorithm, 4 iterations, 28 subsets, 4.8mm Hanning 3D filter) were used for frame-by-frame realignment. The

absence of attenuation correction results in a less biased distribution of tracer, providing a visibly clearer image of the brain, especially around the scalp, whilst the iterative algorithms provide good signal to noise ratios. Frames within the first scanning session (0-30 minutes) were realigned to frame 21, and frames from the last two sessions were aligned to the first frame in that session. A mean image within each scanning session was created, and all frames within the scanning session were aligned again to the mean image. The mean image was then recalculated. This process was performed for each of the three scanning sessions independently. Between-sessions realignment was performed using the co-register routine in SPM. The mean images from the last two scanning sessions were realigned to the mean image from the first session, and those parameters were then applied to all the frames in the corresponding session. This realignment approach ensures all frames, in all sessions, are aligned together.

These transformations were then applied to attenuation corrected (AC) filtered back projected (FBP, fourier-rebinned 2D reconstruction, with geometric, deadtime, scatter and random correction, 4.8 Hanning Transaxial filter) PET images, which were used for quantification in order to avoid bias from the AC-iterative images. The transformations were also applied to AC-iterative PET images (4 iterations, 28 subsets, 4.8mm Hanning 3D-filter), which were used for warping atlases, due to their good signal to noise ratio and good contrast between brain structures. All images were reconstructed to 128 x 128 x 47 voxels with dimensions 2 x 2 x 3.27mm. The pre-processing procedure is illustrated in Figure 2.4.

Defining the Regions of Interest

Region of Interest (ROI) analysis is a standard approach to the analysis of PET data. A computer is used to draw a region around a contiguous set of pixels in the add-image (a summated PET image), using image analysis software (Analyze; Biomedical Imaging Resource, Mayo Foundation). For example, a standard template for the caudate nucleus is generally defined by 5mm x 7mm ellipse. Time-activity curves are then produced that plot the mean radioactivity value in a ROI across a sequence of PET images (i.e. across time). An alternative approach is to use ROI templates that have been defined on a magnetic resonance (MRI) scan positioned in standard Montreal Neurological Institute (MNI) space (Meyer et al., 1999), and to

spatially transform this to the individual space for each scan, using an automated (spatial normalisation) procedure. This standardizes the image analysis and removes any subjectivity in the placing of ROIs. The latter approach was used for the current study. Details of the specific ROIs will be discussed in the relevant results chapters. In general, the cerebellar reference region was defined using the Automated Anatomical Labelling Atlas (Tzourio-Mazoyer et al., 2002) due to its clearer definition of the cerebellum without the vermis, and the Tziortzi Atlas (Tziortzi et al., 2011) was used to define the caudate, putamen and specified extrastriatal regions (detailed in Chapters 4 & 5). An additional atlas was used to define the striatal subdivisions (as discussed in Chapter 1, Section 1.2.1).

Defining the Striatal Subdivisions

Recent advances in the spatial resolution of PET cameras have enabled imaging techniques to differentiate between anatomical subregions of the striatum, as opposed to analysing the striatum as a whole. This technique was first demonstrated in a study which showed increased amphetamine-induced dopamine release in the ventral striatum (nucleus accumbens, ventromedial caudate, and anteroventral putamen) compared to the dorsal caudate, in both baboons and humans (Drevets et al., 2001; Drevets et al., 1999). The consistency of these findings with microdialysis data in non-human primates (Di Chiara et al., 1993) supports the ability of PET imaging to quantify binding in subregions of the striatum. The adaptation of data from detailed neuroanatomical studies in experimental animals (Haber et al., 2000) for use in PET (Mawlawi et al., 2001) have now made it possible to quantify tracer binding in the striatum in terms of its functional connections - limbic, associative, and sensorimotor regions - referred to as the functional subdivisions. The feasibility and validity of such techniques have been evaluated (Martinez et al., 2003; Mawlawi et al., 2001), and a gradient of D2/3 receptor binding consistent with post-mortem studies has been reported. The greatest BP_{ND} is reported in the sensorimotor striatum and the lowest values in the limbic striatum (Mawlawi et al., 2001). The same gradient has also been reported in an AD sample (Reeves et al., 2009). Imaging of the striatal functional subdivisions could enable us to further explore the underlying pathophysiology of psychotic symptoms in AD, and the contribution of regional D2/3 occupancy to therapeutic response.

The template used in the current study for the three striatal subdivisions was originally defined on a magnetic resonance (MRI) scan positioned in standard MNI space (Hammers et al., 2003; Meyer et al., 1999), using the same anatomical landmarks described by Mawlawi et al. (2001). This template has been previously used to quantify [^{11}C]raclopride BP_{ND} in people with AD (Reeves et al., 2009), and is shown in Figure 2.5. The boundary between the ventral (limbic) striatum (inferiorly) and dorsal caudate and dorsal putamen (superiorly) was defined using the anterior commissure-posterior commissure (AC-PC) transaxial plane. The ventral (limbic) striatum was sampled from the anterior boundary of the striatum to the level of the anterior commissure coronal plane. The transaxial AC-PC plane was used to subdivide the dorsal caudate and putamen into associative (caudate and putamen rostral to the anterior commissure and the caudate caudal to the anterior commissure) and sensorimotor (putamen caudal to the anterior commissure) striatum.

Warping via PET Image

The next stage in the analysis involved warping the atlases to subject space via a previously constructed PET [^{18}F]fallypride template in standard (MNI) space. The current study chose not to co-register MRI with PET data, as the specific aim was to establish the most widely applicable analysis method that would be suitable for use in older, cognitively impaired individuals, in whom MRI may be contraindicated or difficult to tolerate. The [^{18}F]fallypride template was created from six healthy young subjects (Dunn et al., 2010) using structural MRI data which had been spatially normalised to MNI space using the unified segmentation algorithm in SPM. The transformations were applied to each of the co-registered summed (3-30 minutes) AC-iterative PET images, as these reconstructions have a good signal to noise ratio, and show a clear distribution of [^{18}F]fallypride across the brain during the first 30 minutes. A mean [^{18}F]fallypride template was calculated by scaling each transformed PET image by the subject global mean, and then taking the mean of the six PET images.

Add-images for the current study were created, summing frames 21-47 for the pre-treatment protocol, and 21-37 for the post-treatment scan. The [^{18}F]fallypride template was warped to these add-images using the SPM normalisation routine, and the warp parameters were then applied to the atlas.

Model Fitting

Time-activity curves for individual regions (left and right hemispheres combined) were extracted from regions defined by the warped atlases in the realigned and co-registered PET images, and used to estimate tracer kinetic parameters based on the simplified tissue reference model (Lammertsma & Hume 1996). Mathematical modelling was used to estimate the three parameters; relative delivery (R_1), the target region clearance constant (k_2), and BP (the parameter of interest).

Figure 2.4: Flow Diagram of Pre-Processing Method

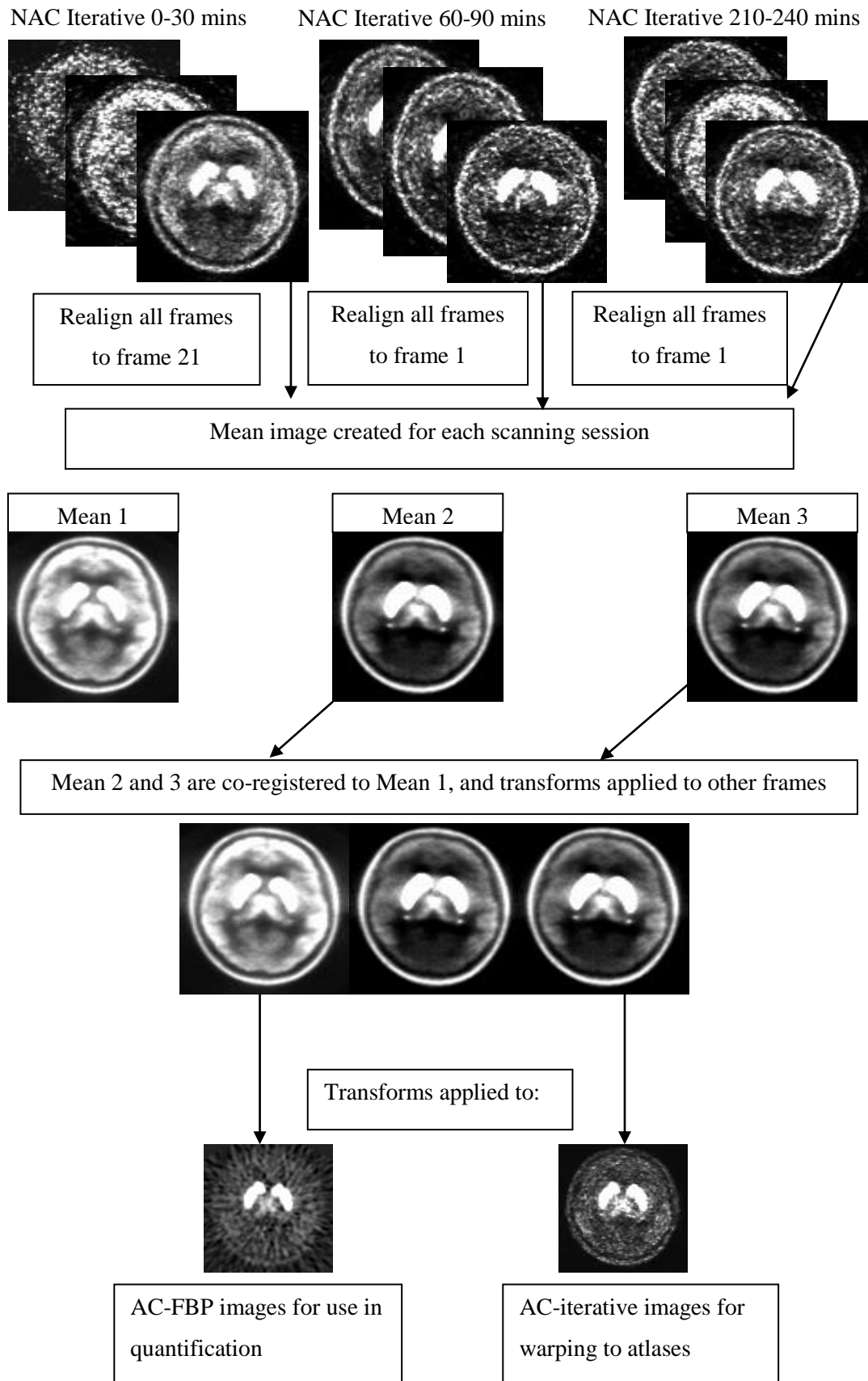
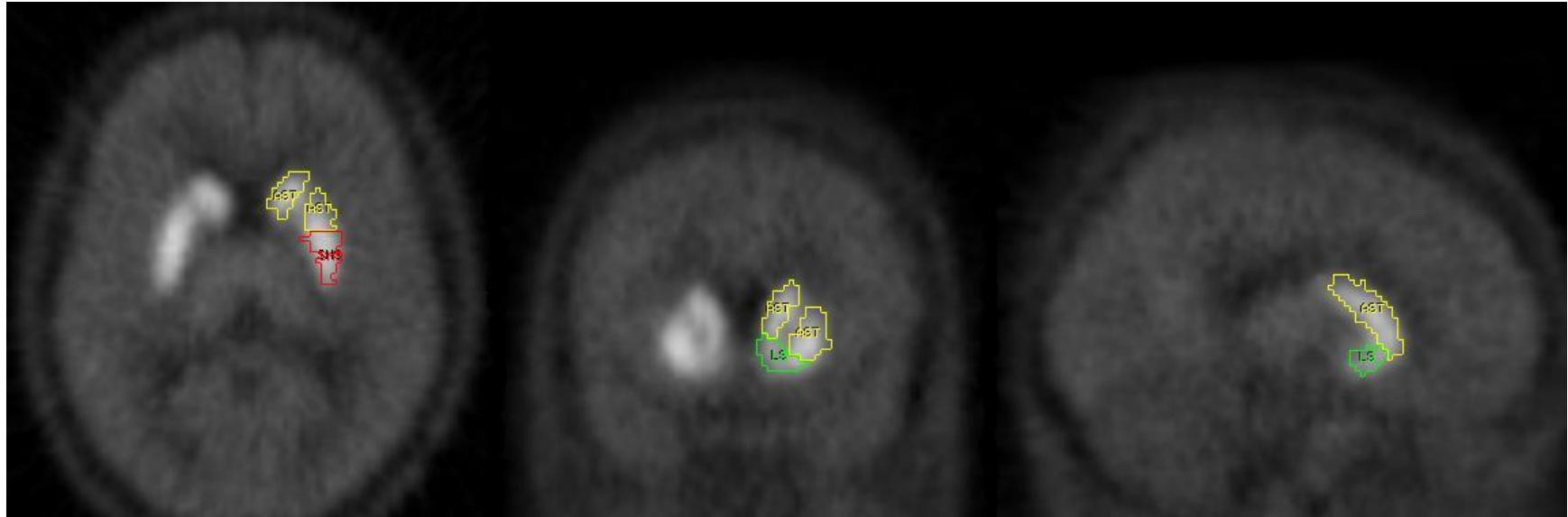


Figure 2.5: Delineation of Striatal Functional Subdivisions



Right-sided sensorimotor (shown in red), associative (shown in yellow) and limbic (shown in green) regions-of-interest, defined on a magnetic resonance (MRI) scan, have been superimposed upon a [^{11}C]raclopride (dynamic) image positioned in standard Montreal Neurological Institute (MNI) space. From left to right: transverse view, sensorimotor striatum and associative striatum; coronal view, associative striatum and limbic striatum; sagittal view, associative striatum and limbic striatum.

Chapter 3: Establishing the Neuropsychological Profile of Psychotic Symptoms in AD

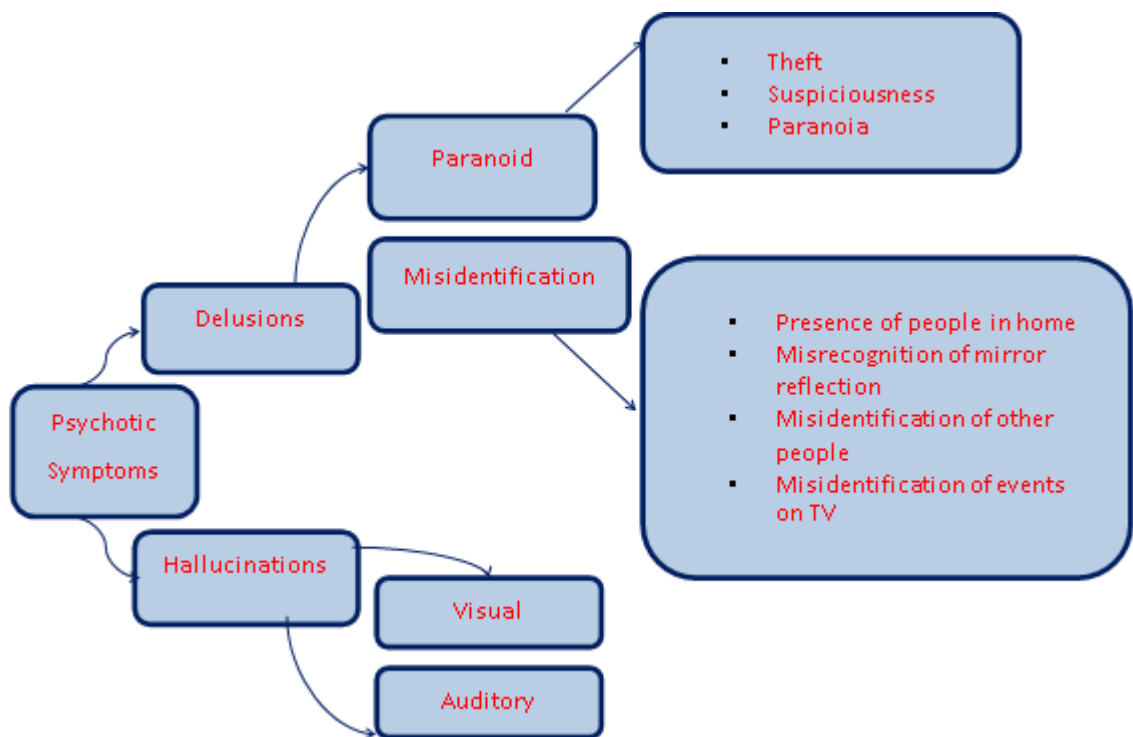
3.1 Introduction

3.1.1 Prevalence and Phenomenology

Psychotic symptoms (delusions and hallucinations) were amongst the first neuropsychiatric symptoms to be described in AD. In his initial case report, Alois Alzheimer described a 51 year old lady who presented with fixed, false ideas that staff were trying to harm her and steal from her (persecutory delusions) and complained of ‘seeing things’ (visual hallucinations) in the context of marked cognitive dysfunction (Alzheimer 1907). It was not until the 1980s that the phenomenology of psychotic symptoms in AD was explored in more depth and symptoms categorised as three principal domains; paranoid delusions, misidentifications, and hallucinations (Figure 3.1, Rubin et al., 1988). Paranoid delusions most commonly involve ideas of ‘theft’ or ‘suspiciousness’ regarding the intentions of others, but may also manifest as morbid jealousy (belief that one’s spouse is having an affair), or beliefs about ‘abandonment’. Misidentification phenomena mostly involve the belief that there is an intruder in the house (phantom boarder syndrome), confusion regarding the identity of one’s reflection in the mirror (Mirror sign), confusion regarding the TV (TV sign), believing that a spouse or relative is an imposter (Capgras syndrome), and not recognising one’s house as one’s own. Hallucinations are primarily visual or auditory in nature and rarely involve modalities. Table 3.1 elaborates on the content of persecutory and misidentification delusions (Reeves et al., 2012). Subsequent studies have largely concurred with this classification (Burns et al., 1990a; Merriam et al., 1988; Reisberg et al., 1987; Teri et al., 1988). Prevalence studies (reviewed by Ropacki & Jeste, 2005) have reported the median prevalence of psychotic symptoms in AD to be 41% (range = 12.2%–74.1%). This includes 36% presenting with delusions, mostly persecutory (reported in 50.9% of studies), and 18% with hallucinations (predominantly visual in nature). Psychotic symptoms in patients with AD are associated with substantial morbidity, including a poorer quality of life (Banerjee et al., 2006; Matsui et al., 2006), an increased frequency of co-morbid agitation (Gilley et al., 1991), verbal and physical aggression (Kotrla et al., 1995) and anxiety (Schneider et al., 2003). Non-cognitive

symptoms of dementia are major contributors to the higher distress observed in patients and caregivers (Deimling & Bass 1986). They are also associated with early institutionalisation (Steele et al., 1990), worse prognosis, and increased costs (Herrmann et al., 2006). It is suggested that an estimated 30% of the financial burden in AD is directly attributable to management of non-cognitive symptoms (Murman & Colenda 2005).

Figure 3.1: Classification of Psychotic Symptoms in AD



Adapted from Rubin et al. (1988)

Table 3.1: Description of Delusional Content in AD

Paranoid delusions	Misidentification phenomena
‘Theft’ – others are stealing from him/her	‘Phantom boarder’ – real or imagined people are staying in the house
‘Harm’ – others are trying to hurt or harm	‘Mirror sign’ – inability to recognise oneself in the mirror
‘Morbid jealousy’ – spouse is having an affair	‘TV sign’ – inability to differentiate between the TV and reality
‘Abandonment’ – family/spouse/carer is planning to abandon him/her	‘Picture sign’ – inability to differentiate between a picture/photograph and reality
	‘Capgras’ – carer has been replaced by an imposter
	‘House is not one’s home’ – inability to recognise one’s home environment
	‘Dead person is alive’ – calls out, looks for dead spouse or family member

(Adapted from Reeves et al., 2012)

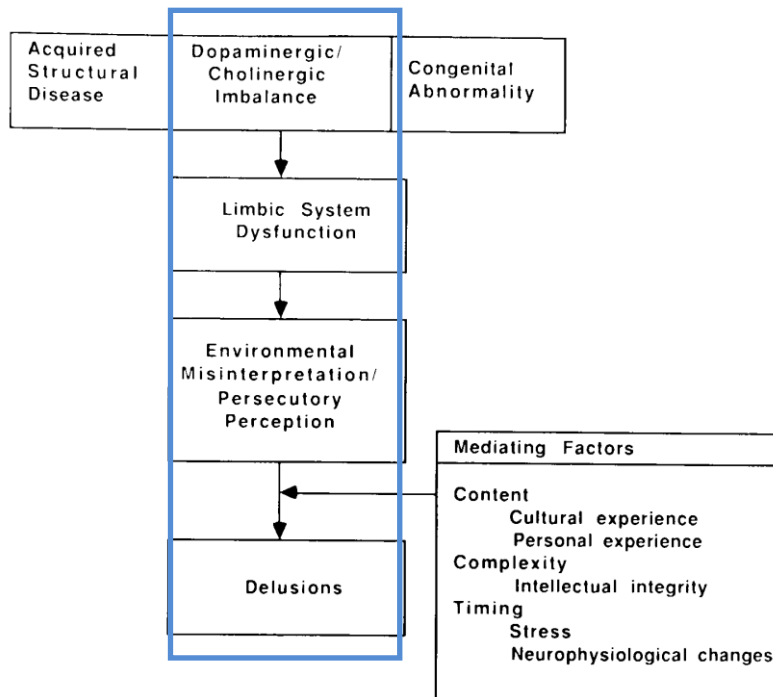
3.1.2 Pathophysiology of Psychotic Symptoms in AD

In the 1980s, an increasing awareness of the prognostic implications of psychotic symptoms in AD led to an exploration of the underlying pathophysiology of delusions and hallucinations. Cummings and Victoroff (1990) discussed four possible theories, which attributed psychotic symptoms in AD to: (i) efforts to understand the environment within the context of cognitive deficits, (ii) mood changes, (iii) coincidence, and (iv) neurobiological changes. The first of these theories originated from suggestions that delusions may reflect the patient’s efforts to explain misplaced possessions (Rabins et al., 1982). However, this explanation is challenged by reports of delusions occurring prior to identifiable cognitive deficits in AD, although this may be due to a lack of sensitivity of neuropsychological tests to detect subtle changes in cognition. Nevertheless, the poor correlation of dementia severity with the presence of delusions also argues against the first theory (Cummings et al., 1987). Furthermore, the lack of correlation between the intensity of mood changes and the occurrence of delusions in AD is inconsistent with the theory that mood disturbance underlies psychotic symptoms (Cummings et al.,

1987). Both the high prevalence of psychotic symptoms in AD compared to healthy older adults and reports of dementia as the greatest risk factor for psychosis in the elderly, challenge the assumption that psychotic symptoms in AD occur as a coincidence of old age (Cummings et al., 1987; Miller & Lesser 1988). Neurobiological theories quickly predominated and have been elaborated over the past two decades. Several theories have been suggested, indicating structural (Bruen et al., 2008; Geroldi et al., 2000), neuropathological (Farber et al., 2000; Zubenko et al., 1991), and genetic (Nacmias et al., 2001; Sweet et al., 2010) underpinnings to psychotic symptoms in AD.

The most influential model was proposed by Cummings et al. (1992), which combined anatomical and biochemical explanations, and proposed that limbic dysfunction was a crucial ‘common factor’ across a range of neurological diseases in which psychotic symptoms featured. The limbic dysfunction described was underpinned by a range of insults, including lesions in the temporal lobe or caudate nuclei, or by disruption of the cholinergic/dopaminergic axis. In AD, dopaminergic transmission is relatively preserved in the context of a severe deficiency in cholinergic function, resulting in an imbalance of the two neurotransmitters. Cholinergic deficiency in AD is most severe in limbic regions (Procter et al., 1988), hence the proposed disruption to this region in the formation of psychotic symptoms. Figure 3.2 describes the model, in which a disruption to the limbic surveillance mechanism leads to environmental misperception and interferes with the assessment of environmental threats; incorrectly perceiving danger and threatened behaviour. These perceptual disturbances manifest as the persecutory and misidentification delusions commonly seen in AD. The precise content of the delusions is influenced by an individual’s repertoire of experiences. Support for the cholinergic/dopaminergic theory has come from studies involving anticholinergic agents or amphetamine, which indicate that either cholinergic hypofunction or dopamine excess play a role in delusions (Dysken et al., 1978; Janowsky & Risch 1979). This theory also overlaps with contemporary theories (Kapur 2003), which propose that hyperdopaminergia leads to the ‘aberrant assignment of salience to external objects and internal representations’, ultimately leading to paranoia and delusions.

Figure 3.2: Proposed Pathogenesis of Delusions Arising From Limbic System Dysfunction

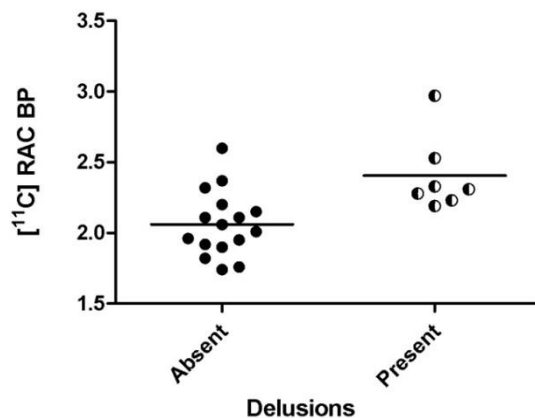


(Cummings 1992)

Further support for the dopaminergic theory of psychotic symptoms has come from neuroimaging techniques such as PET, which are able to visualise striatal D2/3 receptors *in vivo*. The majority of research in this area has focused upon young adults with schizophrenia, and has provided evidence of increased striatal D2/3 receptor density, independent of the effects of antipsychotic medication (Kestler et al., 2001; Laruelle 1998; Zakzanis & Hansen 1998). This area of research has been largely neglected in people with dementia. In one study, PET imaging using [¹¹C]raclopride showed increased striatal D2/3 receptor availability to be associated with psychotic symptoms (predominantly mild, transient delusions) in AD (Reeves et al., 2009). This study observed a 14% increase in tracer binding in the striatum of delusional patients compared to those without delusions (Figure 3.3), consistent with data on young adults with schizophrenia (Kestler et al., 2001; Laruelle 1998; Zakzanis & Hansen 1998). The findings are also consistent with a study which compared psychotic and non-psychotic patients with bipolar disorder (Pearlson et al., 1995), and are supported by several post-mortem studies which showed an increase in D3 receptor availability in those with psychotic symptoms in AD (Sweet et al.,

2001), and in schizophrenia (Gurevich et al., 1997). Taken together, these findings are supportive of a shared dopaminergic aetiology of delusions, and warrant further exploration (reviewed by Reeves et al. (2012) – discussed in Chapter 6, Section 6.3.1).

Figure 3.3: Increased Striatal D2/3 Receptor Availability Associated with Delusions in AD



(Reeves et al., 2009)

3.1.3 Cognitive Correlates of Psychotic Symptoms in AD

Studying the neuropsychological correlates of psychotic symptoms in AD provides an additional method of gaining a more thorough understanding of the underlying pathophysiology. It may help to identify markers that may herald the onset or predict progression of psychotic symptoms, and may potentially identify discrete functional networks involved in the pathophysiology of these symptoms. Defining a neuropsychological profile for psychotic symptoms in AD has, however, proved challenging due to the many inconsistencies reported in the literature. Many studies have reported more severe cognitive impairment in those with psychotic symptoms compared to those without, based on MMSE score (Bassiony & Lyketsos 2003; Fischer et al., 2006; Gilley et al., 1991; Jeste et al., 1992; Mizrahi et al., 2006). However, this is a global measure of cognition and in order to determine the underlying pathology of such psychotic symptoms, more specific cognitive profiling must occur.

Confounding factors such as age, education level and dementia severity (as measured by a global cognitive measure such as the MMSE) need to be carefully controlled for when comparing neuropsychological test performance. If not already controlled for in the recruitment stage (e.g. matched case-control designs), confounding variables such as these must be taken into account during the analysis stage in order to prevent the misinterpretation of results. The importance of controlling for these effects is demonstrated by studies in which impairments in verbal fluency in the psychotic group fail to remain significant after controlling for dementia severity (Chen et al., 1998; Perez-Madriñan et al., 2004). Such results suggest that the differences seen between psychotic and non-psychotic groups were due to differing levels of global cognitive decline, rather than executive functioning per se. Focusing solely on those studies which have controlled for potential confounding effects, executive function deficits have been reported in those with psychotic symptoms, as measured by the Clock Drawing Task (Heinik et al., 2001), and a Frontal Assessment Battery (FAB; tests of conceptualisation, mental flexibility, inhibitory control, motor programming and sensitivity to interference) (Nagata et al., 2009). In contrast, improved attentional performance on the attention/calculation subset of a modified MMSE has been reported in those with psychotic symptoms in AD, compared to those without (Bylsma et al., 1994). Delusions have also been associated with episodic confabulation, a falsification of memory typically associated with frontal lobe dysfunction (Fischer et al., 1995; Johnson et al., 1997; Moscovitch & Melo 1997), both in a group who exhibited delusions and aggression (Lee et al., 2007), and in those with delusions alone (Lee et al., 2009). However, in contrast to the above studies, much of the literature reports negative findings on the association of psychotic symptoms with tasks of executive function, memory, language, and visuospatial function (Migliorelli et al., 1995; Mizrahi et al., 2006; Perez-Madriñan et al., 2004; Starkstein et al., 1994).

Another potentially confounding factor in the analysis of neuropsychological test performance is the use of past or present psychotropic medication. Only two of the above studies adequately controlled for this, either by excluding subjects who had taken psychotropic medication within the 3 weeks prior to assessment (Chen et al., 1998), or by excluding subjects on the basis of past or present psychotropic use (Mizrahi et al., 2006). In contrast, Nagata et al. (2009) excluded patients taking

Cholinesterase Inhibitors (ChEI), however made no mention of psychotropic medication (Nagata et al., 2009). The inconsistencies amongst studies makes it difficult to compare results and to reach any substantial conclusions about the cognitive correlates of psychotic symptoms in AD, given that psychotropic medication may interfere with cognition and/or dopamine transmission.

One way of improving the consistency of reported neuropsychological correlates of psychotic symptoms in AD may be to use a more hypothesis-driven approach to the choice of cognitive domains tested. After finding an association between increased striatal D2/3 availability and delusions in AD (Figure 3.3), Reeves et al. (2010) used the same sample to demonstrate that increased striatal dopaminergic D2/3 receptor activity (as measured by [¹¹C] RAC binding) was also associated with specific aspects of cognitive and motor function, including increased motor speed and poorer attentional performance (recorded as the number of accurate responses on a task of Rapid Visual Processing (RVP)). These results are illustrated in Figures 3.4 & 3.5, respectively. The findings suggest that specific aspects of neuropsychological test performance may differ between psychotic and non-psychotic patients with AD because of their inherent links with dopaminergic neurotransmission. If this were found to be the case, such tests may be more sensitive markers of psychotic symptoms in AD than standard neuropsychological test performance measures, and could potentially be utilised to monitor the functional consequences of D2/3 antagonism by antipsychotic medication. Given that the entire sample of the above study experienced persecutory as opposed to misidentification delusions, it is unclear whether or not the tests may be cognitive markers of the psychosis phenotype or more specifically persecutory delusions, prompting a discussion of psychotic subtypes later in this chapter.

Figure 3.4: Scatter Plot Showing Correlation Between Striatal [^{11}C] RAC Binding (i.e. measure of D2/3 receptor availability) and Performance on Motor Latency Task

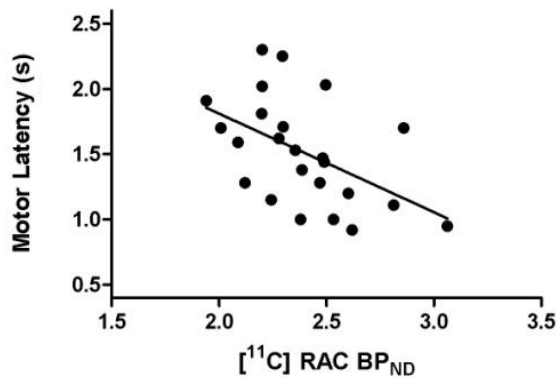
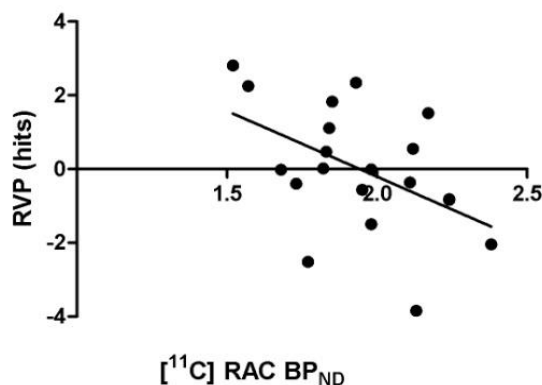


Figure 3.5: Scatter Plot Showing Correlation Between Striatal [^{11}C] RAC Binding and Performance on RVP Task (higher score indicates better attentional performance)



(Reeves et al., 2010)

Regression analysis is a common method used to determine whether certain cognitive tasks are sensitive markers of psychotic symptoms in AD. For example, regression models, such as logistic regression, allow the researcher to determine the effects of multiple independent variables on an outcome measure, and hence are widely used to determine predictor variables, whilst controlling for several potentially confounding variables. Previous studies which have used this technique have identified the total score on the FAB (Nagata et al., 2009), a task of executive function (Hopkins & Libon 2005), and the total MMSE score (Mizrahi et al., 2006), as predictors of psychotic symptoms in AD. Performing regression analysis on

hypothesis-driven neuropsychological tests would provide additional information regarding the suitability of specific tests to act as cognitive markers of psychotic symptoms in AD.

3.1.4 Psychosis Versus Delusional Subtypes

Following the initial report of psychotic symptoms in AD (Alzheimer 1907), the literature classified such symptoms as ‘senile psychosis’, which referred to psychosis in elderly patients with dementia (Jeste & Finkel 2000). An abundance of research was seen in this area in subsequent years, providing clear evidence that the psychotic symptoms and associated features seen in AD were different to those of other dementias and brain disorders with psychotic symptomatology. For example, compared to the complex and bizarre delusions reported in schizophrenia, the delusions reported in AD are more simple and typically of the paranoid type, whilst hallucinations are predominantly visual in AD compared to a high frequency of auditory hallucinations in schizophrenia (Jeste & Finkel 2000). Such differences, together with the distinct phenotype associated with psychotic symptoms in AD, i.e. more rapid cognitive and functional decline, and increased liability to aggressive behaviour (Ropacki & Jeste 2005; Scarmeas et al., 2005), led to psychosis in AD being classified as a distinct syndrome, with individual diagnostic criteria (Jeste & Finkel 2000). In support of a distinct phenotype, several studies reported a suggestive genetic link underlying the presence of psychotic symptoms in AD (Sweet et al., 2010; Sweet et al., 2003).

However, in contrast to the global view of psychotic symptoms, some authors view delusions and hallucinations as distinct phenotypes with separate clinical correlates (Ballard et al., 1995; Bassiony & Lyketsos 2003; Bassiony et al., 2000). Clinical factors such as older age, depression, aggression and poorer general health have been associated with delusions (Bassiony & Lyketsos 2003; Bassiony et al., 2000), while factors such as visual impairment, less education, more severe dementia, longer duration of illness, and falls have been linked to hallucinations (Ballard et al., 1995; Bassiony et al., 2000). Separate neurobiological correlates have also been reported, for example the involvement of the occipital lobes helps to distinguish visual hallucinations from other psychotic symptoms (Casanova et al., 2011).

Others argue, however, for distinct subtypes of delusions, given the diversity of false beliefs reported in AD. As mentioned previously, psychotic phenomena were initially classified into three broad domains; paranoid delusions, misidentification delusions and hallucinations, based on qualitatively similar content (Drevets & Rubin 1989; Rubin et al., 1988). Research into whether these classifications form distinct subtypes of psychotic symptoms in AD is limited, however the low correlation (0.12) reported between paranoid and misidentification delusions (Devanand et al., 1992) is suggestive of independently occurring phenomena.

More recently, factor and cluster analyses were applied to the psychosis items from the CERAD Behavioural Rating Scale (CBRS) (Tariot 1996), in order to identify the subtypes of psychotic symptoms in AD (Cook et al., 2003). The results from this study suggested that symptoms loaded onto two factors, which the authors described as 'paranoid' (persecutory delusions and delusions of abandonment) and 'misidentification' (misidentification delusions and/or visual hallucinations) subtypes (Cook et al., 2003). This classification identifies more homogenous groups for analysis, and has since been used by a number of researchers examining the neurobiological and neuropsychological correlates of psychotic symptoms (Perez-Madriñan et al., 2004; Wilkosz et al., 2006). Such studies indicate that the two subtypes may be characterised by different cognitive trajectories, with frequent reports of a lower MMSE score in patients with misidentification delusions and/or hallucinations (Devanand et al., 1992) but not persecutory delusions (Burns et al., 1990a; Perez-Madriñan et al., 2004), when compared to non-psychotic AD patients. However, evidence from longitudinal data suggests that lower MMSE scores may only predict proneness to misidentification phenomena (Devanand et al., 1997; Wilkosz et al., 2006). These findings suggest that the paranoid and misidentification subtypes may be both phenomenologically and biologically distinct (Ismail et al., 2011; Reeves et al., 2012). It is also possible that the two subtypes are part of a continuum (discussed by Reeves et al., 2012); persecutory delusions occurring early in the course of the disease, hence showing only subtle differences with non-psychotic groups; and misidentification delusions forming later in the disease progression, presenting with more marked cognitive differences compared to the non-psychotic group. However, cognitive trajectories in relation to delusional subtypes have not yet been explored.

Due to the above mentioned inconsistencies in study design and categorisation of psychotic symptoms, it is only possible to draw broad conclusions from the existing data on the cognitive correlates of psychotic symptoms in AD. Studies which aim to identify the cognitive correlates of the psychotic subtypes in AD may support the classification of the subtypes as distinct entities, and may enhance further investigations of the psychotic symptoms in AD by identifying more homogenous groups for genetic, neuroimaging and post-mortem studies. Focusing analyses on hypothesis-driven tests, such as those intimately linked with dopaminergic function (Reeves et al., 2010) could prove useful in further explaining the pathology underlying psychotic symptoms in AD, and determining whether such pathology is subtype specific. Such research may result in more accurate treatment and monitoring of psychotic symptoms in AD.

3.1.5 Aims

The primary aims were:

1. To test the hypothesis that cognitive tests which correlate with dopamine function will differ between psychotic and non-psychotic AD patients.
2. To establish the neuropsychological profile of psychotic symptoms in AD.

The secondary aims were:

1. To further explore any significant between-group differences in neuropsychological test performance in terms of paranoid (persecutory delusions) and misidentification (misidentification delusions and/or visual hallucinations) subtypes.
2. To examine whether neuropsychological test performance can predict the odds of psychotic symptoms in AD patients.

3.2 Methods

3.2.1 Subjects

The sample has been described previously (Chapter 2, Section 2.1.2).

3.2.2 Neuropsychological Tests

The neuropsychological test battery has been described previously (Chapter 2, Section 2.2.3). Tests of motor speed (simple reaction time, SRT) and sustained attention (rapid visual processing, RVP) were analysed first. These tests were separated from their cognitive domains in order to carry out a more focused, hypothesis-driven, investigation of tests with demonstrated links to dopaminergic function (Reeves et al., 2010). In order to establish a full neuropsychological profile of psychotic symptoms in AD, the remaining neuropsychological test measures were organised into the following cognitive domains: executive function, memory, language, constructional praxis and visuoperceptual function.

3.2.3 Procedure

The procedure has been described previously (Chapter 2, Section 2.2.4).

3.2.4 Statistics

All data were analysed using IBM SPSS Statistics 19. Prior to statistical analysis, data outliers were identified as those values which exceeded 1.5 x the interquartile range for each group for a particular variable, and were replaced with the nearest value for that group. This resulted in 1.3% of values being replaced in the non-psychotic group, and 0.8% of values being replaced in the psychotic group. The alternative procedure of dealing with outliers by deleting the subject's data-point was not used due to the small sample size in the current study.

Prior to performing the analysis, data were checked for normality: skewness and kurtosis z score between -1.96 and 1.96 (Ghasemi & Zahediasl 2012; Kim 2013), homogeneity of variance (Levene's statistic), homogeneity of regression, and linearity between dependent variables and covariates. Data submitted to MANCOVA were also assessed for homogeneity of variance covariance matrices (Box's M Test).

Data which violated both the assumption of normality and homogeneity of variance were transformed to fulfil at least one assumption (Olejnik & Algina 1984). Transformations were as follows, where x represents the test score: MMSE = x^4 ; Delayed Visual Recall = $\log_{10}(x+1)$; Incomplete Letters = x^2 . The transformed scales were used in the analysis, and the means and standard errors (SE) of these variables are reported in the transformed scale. The mean is also reported in the original scale (back-transformed) to enable ease of interpretation and comparison with other test variables in the respective cognitive domains. However, the SE cannot be back-transformed in this way and has therefore not been presented in the original scale (Jørgensen & Pedersen 1998). For comparison, the transformed and untransformed means and SE have been reported in Appendix 7.4.1. Data which violated the assumption of homogeneity of variance were analysed using a stricter alpha level ($p < 0.025$; Tabachnick & Fidell, 2012). Data which violated the assumption of homogeneity of regression were omitted from the analysis.

Between-group differences in demographic data were analysed using independent samples t-tests, with the presence of psychotic symptoms as the grouping variable. Separate MANCOVAs were performed for multiple dependent variables in specific cognitive domains, and ANCOVAs were carried out where there was only one dependent variable in a cognitive domain. The result of each MANCOVA was determined using the Pillai criterion, which is more robust than other options to unequal sample sizes and violations of homogeneity of covariance (Tabachnick & Fidell 2012). Where a MANCOVA resulted in a significant main effect ($p < 0.05$), data were submitted to separate ANCOVAs. Significant differences were determined using a Bonferroni adjusted alpha level, and Fisher's Least Significant Difference test (LSD), to correct for multiple pairwise comparisons. Logistic regression was then applied to tests which showed significant between-group differences, in order to evaluate the extent to which test performance can predict psychotic symptoms.

Data were first analysed using a global approach to psychotic symptoms i.e. those with delusions or hallucinations vs. those with no psychotic symptoms, in order to allow for comparison with a greater number of studies in the literature, and to maximise the sample size in each group. Post-hoc analyses of delusional subtypes were only applied to tests which showed significant between-group differences, so as to avoid type 1 errors through multiple comparisons.

3.3 Results

3.3.1 Prevalence

A total of 80 subjects were recruited to this study. However, upon screening, 10 subjects were excluded on the basis of specified criteria (detailed in Chapter 2, Section 2.1.2): three subjects had an MMSE score of less than 10, one scored above 6 on the GDS-15, three were taking antidepressants at the time of assessment, one had significant cerebrovascular pathology, and two were clinically diagnosed with psychiatric disorders other than AD. Of the remaining 70 subjects, 34 (48.6%) had experienced a psychotic symptom since the onset of memory difficulties. 82% (n = 28) of this group were still presenting with the symptoms at the time of assessment, while 18% (n = 6) reported symptoms as present within the last year.

Table 3.2 details the phenomenology of psychotic symptoms in the sample. The most common occurring delusions were of a persecutory type, primarily involving ideas of theft, and were present in approximately 30% of the sample. Hallucinations occurred in 10% of the sample, and were predominantly visual (7.1%).

Table 3.2: Classification of Delusions

Classification	Content¹	Ever experienced N (%)	Currently experienced N (%)	Total²
Persecutory	In danger/others are planning to hurt him/her	-	1 (1.4)	20 (28.6)
	Others are stealing from him/her	3 (4.3)	17 (24.3)	
	Spouse is having an affair	-	3 (4.3)	
	Family members plan to abandon him/her	-	5 (7.1)	
Misidentification	Unwelcome guests are staying in his/her house	4 (5.7)	6 (8.6)	10 (14.3)
	His/her spouse or others are not who they claim to be	1 (1.4)	4 (5.7)	5 (7.1)
	His/her house is not his/her own	2 (2.9)	6 (8.6)	8 (11.4)
	Television/magazine figures are present in his/her home	-	-	
	Any other unusual beliefs	-	6 (8.6)	
	- Inanimate objects are alive	-	2 (2.9)	
	- He/she has won an award	-	2 (2.9)	
- He/she is part of a police operation	-	1 (1.4)		
- He/she is living in the middle of the war and must escape	-	1 (1.4)		
Hallucinations	He/she can hear voices	-	2 (2.9)	5 (7.1)
	Talks to people who are not there	-	1 (1.4)	
	Seeing things not seen by others	1 (1.4)	4 (5.7)	
	Smells odours not smelled by others	-	-	
	Feel things on his/her skin	-	-	
	Tastes without known cause	-	-	
	Any other unusual sensory experiences	-	-	

Note: Some subjects experienced multiple delusions within and across each classification. ¹Content taken from subscales of NPI. ²Ever experienced + currently experienced (only presented if different from currently experienced).

Psychotic symptoms were further grouped into two specific subtypes, based on the classification described by Cook et al. (2003); Paranoid only and Misidentification only. Subjects experiencing both types of delusions were grouped into a third subtype; Paranoid and Misidentification. Table 3.3 shows the frequency of each subtype within the sample. The highest proportion (20%) of the sample reported only the paranoid subtype, while approximately 17% were grouped in the misidentification subtype, and only 8 (11.4%) subjects exhibited both subtypes.

Table 3.3: Psychotic Subgroups			
Group	Male N	Female N	Total N (%)
Non-Psychotic	16	20	36 (51.4)
Psychotic	16	18	34 (48.6)
- Paranoid only	6	8	14 (20.0)
- Misidentification only	7	5	12 (17.1)
- Paranoid & Misidentification	3	5	8 (11.4)
Total	32	38	70

3.3.2 Demographics

Demographic data on psychotic and non-psychotic subjects are described in Table 3.4. The psychotic group were older ($t_{(68)} = -2.67$, $P = 0.01$) and had a lower estimated Premorbid IQ ($t_{(68)} = 2.34$, $P = 0.02$) than the non-psychotic group, but there were no differences in years of education or MMSE ($t = 0.31$, $p = 0.76$; $t = 1.78$, $p = 0.08$ respectively).

Table 3.4: Demographics

	Group	Mean	SE	T-value	P-value
Age	Non-Psychotic	79.53	0.86	-2.67	0.01*
	Psychotic	82.82	0.89		
Years of Education	Non-Psychotic	9.97	0.27	0.31	0.76
	Psychotic	9.85	0.99		
MMSE ^t (out of 30)	Non-Psychotic	3.48x10 ⁵ (24.3) ^b	1.71x10 ⁵	1.78	0.08
	Psychotic	2.68x10 ⁵ (22.8) ^b	2.03x10 ⁵		
NART errors (out of 50)	Non-Psychotic	20.28	1.95	-2.28	0.03*
	Psychotic	26.38	1.82		
Estimated Premorbid IQ (from the NART)	Non-Psychotic	104.56	1.45	2.34	0.02*
	Psychotic	99.71	1.49		
UPDRS (cut off score <8)	Non-Psychotic	0.00	0.00	-3.04	<0.01*
	Psychotic	0.32	0.11		

Note: n = 36 in non-psychotic group and n = 34 in psychotic group. ^tData transformed to fulfil homogeneity of variance assumption, mean and SE in transformed scale (x⁴). ^bBack-transformed mean. * Significant at p<0.05.

3.3.3 Neuropsychological Test Scores

Unless stated otherwise, age was included as a covariate in ANCOVAs or MANCOVAs. MMSE and number of years of education were also included as covariates, in order to control for the potentially confounding effects of global cognitive level, and educational level. NART errors (and hence estimated premorbid IQ) were not included as a covariate since performance on this test can be affected by the severity of dementia (Taylor 2000). The UPDRS was used solely as a screening tool, and was not included as a covariate as all participants scored below the cut-off score of 8 out of 20.

Hypothesis-Driven Tasks

Adjusted means, standard errors (SE), standard deviations (SD), between-group comparisons and estimated effect sizes (η_p^2) for the two hypothesis-driven tasks are shown below.

Motor Speed

The main effect of the presence of psychotic symptoms on motor speed failed to reach statistical significance ($F_{(1,64)} = 1.40$, $p = 0.24$, $\eta_p^2 = 0.02$).

Table 3.5.1: Motor Speed - Analysis of Covariance

Test	Group	Mean	SE	SD	F-ratio	P-value	η_p^2
Simple Reaction Time (seconds)	Non-Psychotic	431.48 ^a	21.49	128.92	1.40	0.24	0.02
	Psychotic	469.54 ^a	22.51	129.32			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education. $n = 33$ in psychotic group as one subject was unable to complete this task. Exclusion of subjects not currently experiencing psychotic symptoms ($n = 6$) made no difference to the findings (see Appendix 7.3.2, Table 2).

Sustained Attention

There was a significant main effect of the presence of psychotic symptoms on this task of sustained attention ($F_{(1,60)} = 6.91$, $p = 0.01$, $\eta_p^2 = 0.10$). Those with psychotic symptoms achieved fewer correct responses compared to the non-psychotic group, suggesting poorer sustained attention in the psychotic group. Age was not included as a covariate due to it violating the homogeneity of regression assumption.

Table 3.5.2: Sustained Attention - Analysis of Covariance

Test	Group	Mean	SE	SD	F-ratio	P-value	η_p^2
Rapid Visual Processing (accurate responses out of 24)	Non-Psychotic	19.07 ^a	0.71	4.14	6.91	0.01*	0.10
	Psychotic	16.32 ^a	0.76	4.15			

Note: ^aAdjusted mean with constant covariates - transformed MMSE and years of education. $n = 30$ in psychotic group as four subjects were unable to complete the task, and $n = 34$ in non-psychotic group as two subjects were unable to complete this task. *Significant main effect at $p < 0.05$. Exclusion of subjects not currently experiencing psychotic symptoms ($n = 6$) made no difference to the findings (see Appendix 7.3.2, Table 3).

Neuropsychological Correlates of Psychotic Symptoms in AD

Adjusted means, standard errors (SE), between-group comparisons and estimated effect sizes (η_p^2) for the executive function, memory, language, praxis and visuoperceptual domains are displayed in tables 3.5.3 to 3.5.7 respectively. The SD is also reported for analyses which reached statistical significance.

Executive Function

The main effect of the presence of psychotic symptoms on tasks of executive function failed to reach statistical significance ($F_{(1,55)} = 0.89$, $P = 0.51$, $\eta_p^2 = 0.10$). Age was not included as a covariate due to it violating the homogeneity of regression assumption.

Table 3.5.3: Executive Function - Multivariate Analysis of Covariance

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Semantic Fluency (number of words)	Non-Psychotic	22.47 ^a	1.07	0.89	0.51	0.10
	Psychotic	20.92 ^a	1.25			
Phonemic Fluency (number of words)	Non-Psychotic	25.03 ^a	1.72			
	Psychotic	26.15 ^a	2.02			
Digit span (maximum = 30)	Non-Psychotic	13.34 ^a	0.41			
	Psychotic	12.89 ^a	0.48			
Hayling Inhibition time (seconds)	Non-Psychotic	127.31 ^a	10.27			
	Psychotic	106.38 ^a	12.01			
Hayling total errors (maximum = 15)	Non-Psychotic	9.75 ^a	0.63			
	Psychotic	10.39 ^a	0.74			
Go/No-Go Probability of Inhibition (%)	Non-Psychotic	79.42 ^a	1.98			
	Psychotic	78.81 ^a	2.31			

Note: ^aAdjusted mean with constant covariates - transformed MMSE and years of education. n = 25 in psychotic group as nine subjects were unable to complete at least one of the tasks from this cognitive domain, and n = 34 in non-psychotic group as two subjects were unable to complete at least one of the tasks. Exclusion of subjects not currently experiencing psychotic symptoms (n = 6) made no difference to the findings (see Appendix 7.4.2, Table 4).

Memory

The main effect of psychotic symptoms on memory failed to reach statistical significance ($F_{(1,65)} = 0.88$, $P = 0.50$, $\eta_p^2 = 0.07$).

Table 3.5.4: Memory - Multivariate Analysis of Covariance

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Immediate Verbal Recall (maximum = 30)	Non-Psychotic	10.21 ^a	0.52	0.88	0.50	0.07
	Psychotic	11.19 ^a	0.53			
Delayed Verbal Recall (maximum = 10)	Non-Psychotic	1.07 ^a	0.23			
	Psychotic	1.43 ^a	0.24			
Delayed Visual Recall ^t (maximum = 14)	Non-Psychotic	0.39 ^a (1.45) ^b	0.06	0.06	0.06	
	Psychotic	0.31 ^a (1.04) ^b	0.06			
Delayed Verbal Recognition (maximum = 20)	Non-Psychotic	15.43 ^a	0.49			
	Psychotic	16.11 ^a	0.51			
Delayed Visual Recognition (maximum = 25)	Non-Psychotic	17.37 ^a	0.58			
	Psychotic	16.97 ^a	0.60			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education.

^tData transformed to fit homogeneity of variance assumption, mean and SE in transformed scale $\log_{10}(x+1)$. ^bBack-transformed mean. Exclusion of subjects not currently experiencing psychotic symptoms ($n = 6$) made no difference to the findings (see Appendix 7.4.2, Table 5).

Language

The main effect of the presence of psychotic symptoms on language failed to reach statistical significance ($F_{(1,65)} = 0.42$, $P = 0.52$, $\eta_p^2 = 0.01$).

Table 3.5.5: Language - Analysis of Covariance

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Boston Naming Test (maximum = 15)	Non-Psychotic	11.58 ^a	0.42	0.42	0.52	0.01
	Psychotic	11.18 ^a	0.43			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education.

Exclusion of subjects not currently experiencing psychotic symptoms ($n = 6$) made no difference to the findings (see Appendix 7.4.2, Table 6).

Constructional Praxis

The main effect of the presence of psychotic symptoms on constructional praxis failed to reach statistical significance ($F_{(1,64)} = 1.63$, $P = 0.20$, $\eta_p^2 = 0.05$).

Table 3.5.6: Constructional Praxis - Multivariate Analysis of Covariance

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Total Praxis score (maximum =11)	Non-Psychotic	9.07 ^a	0.32	1.63	0.20	0.05
	Psychotic	8.25 ^a	0.32			
Clock Drawing Task (scale 1-6, maximum =1)	Non-Psychotic	3.19 ^a	0.21			
	Psychotic	3.51 ^a	0.22			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education. n = 35 in non-psychotic group as one subject was unable to complete at least one of the tasks in this domain. Exclusion of subjects not currently experiencing psychotic symptoms (n = 6) made no difference to the findings (see Appendix 7.4.2, Table 7).

Visuoperceptual Function

There was a significant main effect of psychotic symptoms on visuoperceptual function ($F_{(1,64)} = 4.17$, $P = 0.005$, $\eta_p^2 = 0.25$).

Table 3.5.7: Visuoperceptual Function – Multivariate Analysis of Covariance

Test	Group	Mean	SE	SD	F-ratio	P-value	η_p^2
Incomplete Letters [†] (maximum = 20)	Non-Psychotic	335.83 ^a (18.33) ^b	15.36	92.18	4.17	0.005 [*]	0.25
	Psychotic	263.74 ^a (16.25) ^b	16.09	92.45			
Object Decision (maximum = 20)	Non-Psychotic	15.32 ^a	0.49	2.92			
	Psychotic	13.89 ^a	0.51	2.93			
Number Location (maximum = 10)	Non-Psychotic	7.44 ^a	0.44	2.65			
	Psychotic	6.61 ^a	0.46	2.65			
Cube Analysis (maximum = 10)	Non-Psychotic	6.94 ^a	0.43	2.60			
	Psychotic	6.86 ^a	0.45	2.60			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education. n = 33 in psychotic group as one subject was unable to complete at least one of the tasks in this domain. ^{*}Significant main effect at $p < 0.025$ as Levene's test was significant ($p < 0.001$) for Incomplete Letters. [†]Data transformed to fit normality assumption, mean and SE in transformed scale. ^bBack-transformed mean. Exclusion of subjects not currently experiencing psychotic symptoms (n = 6) made no difference to the findings (see Appendix 7.4.2, Table 8).

Analysis of each individual dependent variable, using a Bonferroni adjusted alpha level of $p < 0.0125$, showed that the presence of psychotic symptoms had a significant effect on performance on the Incomplete Letters task ($F_{(1,64)} = 9.85$, $P = 0.003$, $\eta_p^2 = 0.13$; Table 3.5.8).

Test	F-ratio	P-Value	η_p^2
Incomplete Letters [†] (maximum = 20)	9.85	0.003*	0.13
Object Decision (maximum = 20)	3.88	0.053	0.06
Number Location (maximum = 10)	1.56	0.22	0.02
Cube Analysis (maximum = 10)	0.02	0.90	<0.001

Note: [†]Data transformed to fit normality assumption. *Significant at Bonferroni adjusted alpha level, $p < 0.0125$. Exclusion of subjects not currently experiencing psychotic symptoms ($n = 6$) made no difference to the findings (see Appendix 7.4.2, Table 9).

3.3.4 Post-hoc Analyses of Psychotic Subgroups

Given the significant between-group differences observed in a task of sustained attention and one of visuo-perceptual function, data were further analysed to determine the effect of specific subtypes of psychotic symptoms on task performance.

Sustained Attention: Subgroup Analysis

Adjusted means, SE, SD and a between-group comparison of sustained attention are shown in Table 3.6.1. There was a significant main effect of the subtype of psychotic symptom on sustained attention ($F_{(3,57)} = 3.39$, $p = 0.02$, $\eta_p^2 = 0.15$). Post-hoc Fisher's LSD pairwise comparisons showed that accuracy rates were significantly lower in the misidentification group compared to the non-psychotic group ($p = 0.004$). No other significant between-group differences were observed (Table 3.6.2).

Table 3.6.1: Sustained Attention – Subgroup Analysis of Covariance

Psychotic Subtype	Mean	SE	SD	F-ratio	P-value	η_p^2
Non-Psychotic	19.10 ^a	0.73	4.24	3.39	0.02*	0.15
Paranoid	16.62 ^a	1.21	4.35			
Misidentification	14.74 ^a	1.28	4.24			
Paranoid & Misidentification	18.40 ^a	1.74	4.27			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education. n = 13 in paranoid group and n = 11 in misidentification group as one subject from each group was unable to complete the task. n = 6 in paranoid & misidentification group and n = 34 in non-psychotic group as two subjects from each group were unable to complete the task. *Significant main effect at p<0.05.

Table 3.6.2: Sustained Attention – Posthoc Pairwise Comparisons

Psychotic Subtype A	B	Mean difference (A-B)	SE	P-value
Non-Psychotic	Paranoid	2.49	1.45	0.09
	Misidentification	4.37*	1.48	0.004
	Paranoid & Misidentification	0.71	1.93	0.72
Paranoid	Misidentification	1.88	1.80	0.30
	Paranoid & Misidentification	-1.78	2.08	0.39
Misidentification	Paranoid & Misidentification	-3.66	2.15	0.09

Note: *Significant mean difference at p<0.05. Multiple comparisons corrected for using Fisher's LSD.

Visuoperceptual Function: Subgroup Analysis

Adjusted means, SE, SD and a between-group comparison of visuoperceptual function are shown in Table 3.6.3. There was a significant main effect of the subtype of psychotic symptom on visuoperceptual function ($F_{(3,62)} = 3.54$, $p < 0.001$, $\eta_p^2 = 0.19$). Individual analysis of each dependent variable, using a Bonferroni adjusted alpha level of $p < 0.0125$, showed only the Incomplete Letters task to significantly differ between psychotic subgroups ($F_{(3,62)} = 11.81$, $p < 0.001$; Table 3.6.4). Post-hoc Fisher's LSD pairwise comparisons showed that the score on the Incomplete Letters task was significantly lower in the misidentification subgroup compared to the non-psychotic group ($p < 0.001$), paranoid group ($p = 0.001$), and those with both misidentification and paranoid subtypes ($p < 0.001$). No other significant between-group differences were observed (Table 3.6.5).

Table 3.6.3: Visuo perceptual Function – Subgroup Multivariate Analysis of Covariance

Test	Psychotic Subtype	Mean	SE	SD	F-ratio	P-value	η_p^2
Incomplete Letters	Non-Psychotic	18.23 ^a	0.48	2.88	3.54	<0.001*	0.19
	Paranoid	16.64 ^a	0.78	2.91			
	Misidentification	12.80 ^a	0.82	2.85			
	Paranoid & Misidentification	18.63 ^a	1.08	2.86			
Object Decision	Non-Psychotic	15.33 ^a	0.49	2.95			
	Paranoid	13.41 ^a	0.80	2.99			
	Misidentification	14.40 ^a	0.85	2.93			
	Paranoid & Misidentification	13.96 ^a	1.11	2.94			
Number Location	Non-Psychotic	7.41 ^a	0.43	2.56			
	Paranoid	6.36 ^a	0.69	2.58			
	Misidentification	5.75 ^a	0.73	2.54			
	Paranoid & Misidentification	8.75 ^a	0.96	2.55			
Cube Analysis	Non-Psychotic	6.91 ^a	0.41	2.44			
	Paranoid	7.87 ^a	0.66	2.46			
	Misidentification	5.05 ^a	0.70	2.42			
	Paranoid & Misidentification	8.06 ^a	0.92	2.42			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education. n = 7 in the paranoid & misidentification group as one subject was unable to complete the number location task. *Significant main effect at p<0.025 as Levene's test was significant (p<0.001) for Incomplete Letters.

Table 3.6.4: Visuo perceptual Function – Between Subjects Effects

	Test	F-ratio	P-Value
Psychotic Subtype	Incomplete Letters	11.81	<0.001*
	Object Decision	1.50	0.22
	Number Location	2.78	0.05
	Cube Analysis	3.59	0.02

Note: *Significant with Bonferroni adjusted alpha level, $p < 0.0125$.

Table 3.6.5: Visuo perceptual Function – Posthoc Pairwise Comparisons

Test	Psychotic Subtype		Mean difference (A-B)	SE	P-value
	A	B			
Incomplete Letters	Non-Psychotic	Paranoid	1.59	0.93	0.09
		Misidentification	5.43*	0.96	<0.001
		Paranoid & Misidentification	-0.40	1.21	0.74
	Paranoid	Misidentification	3.84*	1.15	0.001
		Paranoid & Misidentification	-1.99	1.32	0.14
	Misidentification	Paranoid & Misidentification	-5.83*	1.34	<0.001

Note: *Significant mean difference at $p < 0.05$. Multiple comparisons corrected for using Fisher's LSD.

3.3.5 Logistic Regression

To further explore between-group differences observed in sustained attention and visuoperceptual function, logistic regression analysis was performed to determine whether these neuropsychological test measures could act as predictors of psychotic symptoms in AD. First, separate univariate analyses were performed to determine the relationship of each neuropsychological test on the presence of psychotic symptoms, after controlling for age, MMSE score and years of education. Both the RVP and Incomplete Letters task had a significant effect on the presence of psychotic symptoms ($p = 0.03$ and $p = 0.02$, respectively; Table 3.7). Both neuropsychological tests were then entered into a multivariate logistic regression model, with the presence of psychotic symptoms as the dependent variable, and the RVP and Incomplete Letters task as the independent variables. This analysis also controlled for potential confounding effects. Table 3.7 shows the results of the multivariate logistic regression analysis. A total of 64 cases were analysed and the full model was highly significant (chi-squared = 21.34, $df = 5$, $p = 0.001$), accounting for between 28.4 and 37.9% (Cox & Snell and Nagelkerke R Square, respectively) of the variance in psychotic symptoms. The model correctly predicted 73.4% of cases, with a specificity of 76.5%, and sensitivity of 70%. The Wald statistic and P-values demonstrate that performance on the Incomplete Letters task made a significant independent contribution to the prediction of psychotic symptoms ($p = 0.048$). However, performance on the RVP task (sustained attention) did not reach statistical significance for an independent contribution to the prediction of psychotic symptoms in AD ($p = 0.14$). The odds ratio indicates that for each correct response in the Incomplete Letters task, the odds of psychotic symptoms are reduced by a factor of 0.76.

Table 3.7: Logistic Regression

		Odds Ratio	Wald χ^2	P-value
Univariate	Rapid Visual Processing Task	0.85	4.72	0.03*
	Incomplete Letters Task	0.76	5.71	0.02*
Multivariate	Rapid Visual Processing Task	0.89	2.22	0.14
	Incomplete Letters Task	0.76	3.92	0.048*

Note: All logistic regression analyses were controlled for age, MMSE and years of education.

*Significant at $p < 0.05$

3.4 Discussion

The results of the current study showed a statistically significant between-group (psychotic vs. non-psychotic) difference on one of the two hypothesis-driven tests (sustained attention (RVP), not motor latency (SRT)), and also on a task of visuoperceptual function (Incomplete Letters). Post-hoc analyses revealed both significant differences to be driven by the misidentification subgroup of delusions, and the logistic regression analyses showed only the Incomplete Letters task made a significant independent contribution to the prediction of psychotic symptoms. The results are discussed below.

3.4.1 Phenomenology

Of the 34 patients in the psychotic group, 82.4% presented with delusions in the absence of hallucinations. Consistent with the literature, the most common delusional belief involved ideas of theft (Ropacki & Jeste 2005). Phantom boarder syndrome, i.e. the belief that unwelcome guests are in the house, was the most frequently reported misidentification delusion, consistent with previous reports (Burns et al., 1990b). The phantom boarder was variously described as a relative, an unfamiliar individual or somebody who had previously passed away. In the majority of cases, the subjects felt that the phantom boarder meant them no harm, and would repeatedly ask the caregiver whether the person had left yet. However, one subject felt that the phantom boarder intended to harm her and believed she was receiving threatening letters from the unfamiliar individual. The other unusual beliefs listed in Table 3.2 included beliefs that dolls and teddy bears were alive, which led to the subjects talking to and trying to feed the objects. Beliefs from the subjects that they had won an award also occurred, with one man taking his wife to the council's office to collect his award, and another convinced that the queen had awarded him a prize for his services to the chaplaincy. Hallucinations were reported in 10% of the sample, and were predominantly visual (7.1%). The lower prevalence rate of hallucinations compared to delusions is well reported in the literature (Ropacki & Jeste 2005; Savva et al., 2009; Steinberg et al., 2008; Sweet et al., 2010), as is the predominance of visual hallucinations over auditory or other sensory modalities (Ropacki & Jeste 2005).

Using the classification of psychosis suggested by Cook et al. (2003), 20% of the current sample presented with the paranoid subtype, and 17.1% reported the misidentification subtype. Both paranoid and misidentification subtypes were present in a small proportion of subjects (11.4%). The distribution of the paranoid and combined subgroups is comparable to a previous study which aimed to validate Cook et al.'s proposed subtypes (Perez-Madriñan et al., 2004). However, the prevalence rate of those experiencing misidentification phenomena is much lower in the current study's sample (17.1% compared to 26.9%). The increased prevalence of misidentification phenomena reported by Perez-Madriñan et al. (2004) may reflect differences in disease severity between the samples. The mean MMSE score in the psychotic group in the current study was 22.8, compared to a much lower range of 13.4-16.9 reported by Perez-Madriñan et al. These findings are consistent with suggestions that misidentification phenomena occur in the more advanced stages of AD (Burns et al., 1990a; Devanand et al., 1992; Harwood et al., 1999; Harwood et al., 1998) – reviewed by Reeves et al. (2012).

3.4.2 Hypothesis-Driven Tests

The primary aim of this study was to test the hypothesis that tasks which correlate with dopamine function will differ between psychotic and non-psychotic AD patients. The finding that the accuracy of performance on a sustained attentional task (RVP) was significantly poorer in the psychotic group is consistent with previous studies, which found that higher D2/3 receptor availability in patients with mild to moderate AD was associated with both the presence of delusions (Reeves et al., 2009) and poorer performance on this task (Reeves et al., 2010). This is also comparable to studies which report sustained attention deficits in other clinical populations in which dopamine has been implicated, including schizophrenia and ADHD (Bozikas et al., 2005; Stins et al., 2005). Subgroup analysis of the results suggests that the observed differences in test performance between psychotic and non-psychotic groups may be underpinned by the misidentification subtype.

In contrast, the current results are inconsistent with several studies which were unable to detect significant differences between those with and without psychotic symptoms on tasks measuring attention (Jeste et al., 1992; Lee et al., 2007;

Murayama et al., 2009). However, in these latter studies the tests used to assess attention were taken from larger global tests of cognition, such as the Dementia Rating Scale (DRS) and the Cognitive Abilities Screening Instrument (CASI), where the attentional subscales included tasks more specific to working memory (e.g. digit span, repetition and subtraction), as opposed to sustained attention.

Sustained attention has been primarily linked to the prefrontal cortex, with several studies reporting increased cortical [¹⁸F]fluoro-L-dopa (FDOPA) uptake in the dorsolateral prefrontal cortex to be associated with attentional performance (Cabeza & Nyberg 2000). Evidence for the role of dopamine in this region has been provided by pharmacological studies involving stimulant drugs such as amphetamine and methylphenidate which act on dopamine transporters to increase dopamine release, and are currently used as treatment for ADHD (Volkow et al., 2012). In addition, PET imaging studies using [¹¹C]FLB-457 (a selective dopamine D2/3 receptor radiotracer) have shown increases in dopamine release in the frontal cortex (specifically the anterior cingulate cortex) to be associated with sustained attention (Aalto et al., 2005). However, the above literature associates increased dopamine release with *improved* attention. This evidence is contrary to the current findings, which demonstrated poorer attention in the psychotic group, who have a hypothesised hyperdopaminergic state due to cholinergic/dopaminergic imbalance (Cummings 1992). The inconsistency of the literature can possibly be explained by the inverted U-shaped curve of dopaminergic function and cognitive performance (Arnsten 1997; Goldman-Rakic et al., 2000), which suggests that an optimal level of dopaminergic D1 activation in the prefrontal cortex is required for performance of a given cognitive task. The fronto-striatal-thalamic circuitry of the dopaminergic system, specifically the ‘dorsolateral prefrontal’ circuit, may explain the current results, whereby a hyperdopaminergic state in the caudate, as is proposed with the psychotic group in the current sample, could inhibit the inhibitory projections to the thalamus, resulting in an increased excitatory response to the prefrontal cortex. This input may be supra-optimal, resulting in the impaired attentional performance seen in the present results. Support for the argument that increased striatal dopamine D2 receptor function may impair rather than improve attentional performance can be obtained from lesion studies carried out in experimental animals, which have shown that lesions of the striatum may increase the ability to focus upon the relevant

dimensions during an attentional task (Crofts et al., 2001; Roberts et al., 1994). Pharmacological studies which have shown that D2 receptor antagonists improve performance on the stroop task (Williams et al., 1996), and reverse the impairments in performance seen following the use of amphetamine (Van Gaalen et al., 2006), or following lesions of the prefrontal cortex (Pasetti et al., 2003; Pezze et al., 2009), are also consistent with the present findings.

Tasks of sustained attention have been suggested as a marker of vulnerability to schizophrenia, with groups at high risk of developing the disorder also showing impairments on these tasks, including first degree relatives of patients with schizophrenia (Chen et al., 1998), and non-schizophrenic subjects with high schizotypy scores (Lenzenweger et al., 1991). In the current study, the psychotic symptoms reported were mild and transient, with no need for antipsychotic medication. The fact that differences in RVP performance were observed between patients with such mild psychotic symptoms suggests that this may be a sensitive marker of psychosis-proneness in AD. However, it is unclear whether the RVP could be used as a tool to predict the onset of psychotic symptoms in AD, and longitudinal studies would be needed to address this issue directly. Furthermore, the logistical regression analysis suggests that, although the RVP may be able to predict psychosis, the prediction is more likely due to underlying visual aspects of the task, rather than sustained attention itself, given the confounding effect of the Incomplete Letters task in the logistic regression model (see Section 3.4.4).

Contrary to one of the study hypotheses, the difference in motor latency (SRT) between the psychotic and non-psychotic groups did not reach statistical significance. This is at odds with the previously reported finding of an association between motor latency and striatal D2/3 receptor availability in AD (Reeves et al., 2010). The current finding is also inconsistent with the well documented reaction time deficits in disorders in which dopamine has been implicated, including PD (Gauntlett-Gilbert & Brown 1998) and schizophrenia (Nuechterlein 1977).

One of the main differences between the current study and that of Reeves et al. (2010) is the choice of task used to measure motor latency. Reeves et al. used the motor screening test (MOT) from the CANTAB battery (Robbins et al., 1994) as a proxy measure of reaction time. In the MOT, 12 crosses appear on the screen in different locations and the subject is asked to touch each cross as quickly as possible.

In contrast, the current study employed a computerised SRT task, which had the stimulus in a consistent location, and subjects responded via a press pad. A key difference between the two tasks is that subjects are required to direct their gaze and move their finger to a specified location in the MOT, whereas both gaze and hand position remains still in the SRT. It could thus be argued that the additional role of dopamine in saccadic eye movements (Hikosaka et al., 2000) and more marked finger movements enable the MOT to test the role of dopamine in goal directed movement more explicitly than the SRT, therefore making the test more sensitive to detecting changes in dopaminergic function (Reeves et al., 2010). However, analysis of MOT data from the current study (collected as a practice task) showed no significant differences in motor speed between the psychotic and non-psychotic group (see Appendix 7.4.3). This could have been due to motivational effects, given that the subjects knew the MOT was being used as a familiarisation task. However, the present findings could also indicate that motor tasks are not a sensitive measure of psychotic symptoms in AD. It is possible that age-related sensory deficits or osteoarthritis may impact on the ability of motor tasks to measure between-group differences, given that several subjects mentioned some discomfort due to osteoarthritis during the task. This could therefore have masked any differences due to dopaminergic function.

Alternatively, the lack of consistent evidence of dopaminergic function in SRT could explain the present results. Studies reporting no change in SRT performance after pharmacological dopaminergic manipulation in patients with PD has led authors to suggest that SRT may not be exclusively dopamine dependent (Pullman et al., 1990; Starkstein et al., 1989), which is in contrast to the dopaminergic dependence reported in choice reaction time tasks (Pullman et al., 1990). One reason for this could be due to the recruitment of additional attention-demanding processes during the SRT task, which reduces the sensitivity of the task to measure motor latency (Goodrich et al., 1989).

However, the above explanation does not account for the fact that differences were not detected on the MOT in the current study. Another possible explanation for the current results is that motor function and psychotic symptoms in AD are differentially controlled by specific functional subdivisions of the striatum. The MOT task was previously shown to correlate with D2/3 receptor availability in the

sensorimotor striatum, whereas the greatest percentage change in D2/3 receptor availability between those with and without delusions in AD occurred in the associative striatum (Reeves et al., 2009; Reeves et al., 2010). The present finding could therefore imply that tasks associated with dopamine function in the associative striatum are more sensitive cognitive markers of psychotic symptoms in AD, compared to tasks which are predominantly associated with dopamine receptor availability in the sensorimotor striatum. This is supported by the fact that the RVP task, which has previously been shown to correlate with D2/3 availability in the associative striatum (Reeves et al., 2010), was able to detect differences between the psychotic and non-psychotic groups in the current study.

3.4.3 Neuropsychological Correlates of Psychotic Symptoms in AD

A second aim of this study was to establish the neuropsychological profile of psychotic symptoms in AD. Due to the inconsistency of the findings in the literature, the analysis was exploratory rather than hypothesis driven. The present study was unable to detect significant differences between psychotic and non-psychotic subjects on tasks of executive function, memory, language or constructional praxis. There was, however, a significant difference between groups on a task of visuo-perceptual function. Each of the cognitive domains will be discussed in turn below.

Executive Function

The present finding of no significant difference in executive function between the psychotic and non-psychotic group is comparable to the negative findings in much of the literature which used similar tasks to assess this cognitive domain, including digit span (Jeste et al., 1992; Migliorelli et al., 1995; Mizrahi et al., 2006; Perez-Madriñan et al., 2004; Staff et al., 1999; Starkstein et al., 1994), and letter and category fluency (Jeste et al., 1992; Lee et al., 2007; Mentis et al., 1995; Mizrahi et al., 2006; Nagata et al., 2009; Staff et al., 1999; Starkstein et al., 1994). A few studies have reported a significant difference between groups on category fluency (Jeste et al., 1992; Perez-Madriñan et al., 2004) and letter fluency (Chen et al., 1998), however these differences did not remain significant after controlling for MMSE. There is limited

literature on the tasks of verbal and motor inhibition (Hayling Sentence Completion and Go/No-Go task, respectively) in AD, and more specifically in those with psychotic symptoms. However, one study which administered the Go/No-Go task as part of the FAB to psychotic and non-psychotic patients with AD, found a significant between-group difference on the total FAB score, but were unable to detect a significant independent contribution of the Go/No-Go task to the observed differences (Nagata et al., 2009).

Well documented deficits in executive control have been reported in neuropsychiatric disorders in which dopamine has been implicated, including ADHD (Doyle 2006), schizophrenia (Velligan & Bow-Thomas 1999), and PD (Campos-Sousa et al., 2010). It is therefore unexpected that the difference in executive function between those with and without psychotic symptoms in AD failed to reach significance in the current study. One possible explanation for this is that differences in executive abilities between psychotic and non-psychotic AD groups were too subtle to be detected by the tests used in the current study. The executive deficits in disorders linked with dopaminergic function noted above have all been measured in comparison to healthy controls, which would serve to enhance any between-group differences. Alternatively, it is possible that task complexity contributed to the current findings, as nine out of 34 subjects in the psychotic group were unable to complete at least one of the tasks in the executive function domain. This reduction in sample size may have reduced the power of the analysis to detect significant differences between groups.

Memory

The present study failed to detect a significant difference in memory between psychotic and non-psychotic groups. This is comparable to the majority of the literature examining the cognitive profile of psychotic symptoms in AD (Lee et al., 2007; Lopez et al., 1991; Mentis et al., 1995; Migliorelli et al., 1995; Mizrahi et al., 2006; Murayama et al., 2009; Staff et al., 1999; Starkstein et al., 1994). The only studies in which significant differences in memory have been reported between psychotic and non-psychotic groups are those in which differences in potential confounding variables (e.g. MMSE score) have not been accounted for (Jeste et al., 1992, Perez-Madriñan et al., 2004).

Language

The current results show no difference in language abilities between the psychotic and non-psychotic groups, consistent with previous studies, many of which have used the Boston Naming Task (Jeste et al., 1992; Lopez et al., 1991; Mentis et al., 1995; Migliorelli et al., 1995; Mizrahi et al., 2006; Starkstein et al., 1994). Some studies have reported impaired naming (Bylsma et al., 1994), expressive language (Aalten et al., 2007; Potkins et al., 2003), and receptive language (Lopez et al., 1991), in psychotic groups in AD. However, once again these studies did not control for confounding variables such as MMSE score, educational level and depressive illness.

Constructional Praxis

The present finding of no difference in constructional praxis ability between psychotic and non-psychotic groups is consistent with previous studies that have reported no difference between groups on the clock drawing task (Jeste et al., 1992), 'block design' tasks (Jeste et al., 1992; Migliorelli et al., 1995; Mizrahi et al., 2006; Starkstein et al., 1994), and visual construction components from the CASI (Lee et al., 2007). However, it is at odds with that of Heinik et al. (2001), who reported impairments on the Clock Drawing task in those with paranoid and delusional ideation in AD. Several methodological issues could potentially account for this discrepancy between studies. For example, the sample in Heinik et al.'s study was smaller in size, had a lower mean MMSE score (overall mean = 17) compared to the current study (overall mean = 22) and, in addition, failed to fully control for the influence of MMSE score on clock drawing performance between the psychotic and non-psychotic groups. Also, neither the presence of hallucinations nor the use of psychotropic medications were reported by Heinik et al., two factors which might have contributed to the discrepancy between the two studies.

Another factor which might have contributed to the inconsistency of the current results with those of Heinik and colleagues is the use of a different scoring system. The current study used a 6-point scoring system devised by Shulman et al. (1986) (described in Chapter 2, Section 2.2.3), whereas Heinik et al. (2001) used a 15 point

scoring system (Freedman et al., 1994), which may have increased the sensitivity of the test to detect cognitive differences between the groups.

Visuoperceptual Function

Visuoperceptual function was measured by four tasks taken from the VOSP: Incomplete Letters, Object Decision, Number Location and Cube Analysis. The present findings show a significant difference in performance on the Incomplete Letters task between the psychotic and non-psychotic group. The psychotic group performed worse on this task, suggesting impaired visuoperceptual function is a cognitive correlate of psychotic symptoms in AD. A previous study which hypothesized visuoperceptual deficits in those with psychosis in AD reported more perceptual errors in those with high levels of psychosis compared to those with low levels (Hopkins & Libon 2005). This study measured visuoperception in terms of perceptual errors on the Boston Naming Task (such as the patient not identifying pictures accurately), and whole/part errors (such as the patient identifying only one feature or part of the picture). However, the same study failed to show a significant difference between those with and without psychotic symptoms in AD. This finding was contradictory to the study's hypothesis, and the authors suggested that the failure to detect significant between-group differences may have been due to the choice of task - the Boston Naming task may have been insensitive to detect differences between psychotic and non-psychotic groups - or the failure to differentiate between AD and vascular dementia, in which visuoperception is relatively preserved (Sun 2008). There has been other evidence which argues against an association between visuoperception and psychotic symptoms in AD (Lopez et al., 1991; Mentis et al., 1995; Migliorelli et al., 1995; Perez-Madriñan et al., 2004; Staff et al., 1999; Starkstein et al., 1994). However, these studies are limited by small sample sizes ($n < 18$ in psychotic group) (Lopez et al., 1991; Mentis et al., 1995; Staff et al., 1999; Starkstein et al., 1994), and the variety of tasks used, which included Ravens Progressive Matrices and visual form discrimination tasks. This makes direct comparisons between studies difficult, especially given the visuoconstructive component of the drawing tasks.

The fact that the current results identified a between-group difference on only one of the four VOSP tasks (Incomplete Letters) suggests that a specific aspect of

visuoperception may be affected in those with psychotic symptoms in AD. The VOSP measures two forms of perception; object perception (Incomplete Letters and Object Decision tasks), and space perception (Cube Analysis and Number Location tasks). The two forms of perception have been shown to be controlled by separate neurocircuitry, via the ventral and dorsal visual pathways respectively (Mishkin et al., 1983). It could therefore be argued that disruption to the ventral visual pathway may underlie the deficits observed in the psychotic group, given that performance was significantly impaired on the Incomplete Letters task. However, if this were the case, performance would also be impaired on the Object Decision task. The current results do in fact show the psychotic group performed more poorly on this task compared to the non-psychotic group, with the analysis yielding a trend level significance ($p = 0.053$). The inability to detect a significant between-group difference in this task could have been due to statistical power/sample size issues, or the fact that the object decision task had a forced-choice format, which may have masked visuoperceptual impairments by increasing response rates, which in some cases may have been correct by chance.

Subgroup analysis of the results suggests that the observed differences in test performance between psychotic and non-psychotic groups may be mostly accounted for by data from individuals with the misidentification subtype. This finding is consistent with reports of impaired performance on the Incomplete Letters task in patients with delirium and DLB; two disorders in which misperceptions and visual hallucinations are frequently reported (Brown et al., 2009; Cagnin et al., 2013). These results may indicate specific dysfunction in the ventral as opposed to dorsal visual pathway in those with misidentification delusions/hallucinations in AD. The ventral visual pathway, otherwise known as the occipito-temporal pathway, has strong connections to the limbic system, which controls emotions, and the medial temporal lobe, where long-term memories are stored (Suter & Harvey 2011). These connections enable recognition of the perceived object. It has been suggested that disruptions to the ventral visual pathway and/or its connections with the limbic system may be the cause of disorders such as prosopagnosia (the inability to recognise faces) and Capgras syndrome (delusional belief that a familiar person is an imposter) (Breen et al., 2000). Similar pathophysiology may be underlying the misidentification delusions observed in the current sample, given that more marked

pathology has been observed in the limbic regions of this group, but not those with persecutory delusions (Forstl et al., 1994; Mukaetova-Ladinska et al., 1993; Sweet et al., 2000). Given the evidence, it seems plausible that disturbances to the ventral visual pathway may underlie the poorer performance of the misidentification group on the Incomplete Letters task. However, whether the deficits arise due to dysfunction in the ventral visual pathway itself, or its connections with other ventral structures, remains unclear. The dysfunction in the ventral visual pathway may be neurochemical (as discussed in Chapter 6, Section 6.3.1). However, we cannot rule out the possibility that disruption to the ventral visual stream may be caused by pathological changes, for example undetected lewy body formation in the temporal lobe.

That visuoperceptual deficits may lead to misidentification delusions has also been suggested in literature concerning DLB, based on the frequent co-occurrence of visuoperceptual deficits and delusional misidentifications in this disorder (Mori et al., 2000). However, in contrast to suggestions of disruption to the ventral visual pathway, others have postulated that such symptoms may be underpinned by occipital lobe dysfunction, as indicated by neuroimaging studies demonstrating reduced metabolism and blood flow in the occipital lobes in patients with DLB with visuoperceptual dysfunction (Albin et al., 1996; Imamura et al., 1999; Ishii et al., 1998). Consistent with suggestions of occipital involvement is the finding of a significant normalised glucose hypometabolism in the left medial occipital region in those with delusions in AD compared to those without (Hirono et al., 1998), and increased occipital atrophy reported in AD patients with visual hallucinations (Holroyd et al., 2000).

However, the present finding is not supportive of occipital lobe dysfunction, as the deficits observed are specific to the Incomplete Letters task, as opposed to all tasks with visual components. Adding to this, a sensitivity analysis was carried out in order to exclude the possibility of visual sensory deficits in the current results. The analysis was unable to detect a significant difference between subgroups on the VOSP Shape Detection Screening test (a task measuring visual sensory deficits), and is therefore unable to explain the low scores occurring predominantly in the misidentification subgroup. In addition to this, the between-group differences on the

Incomplete Letters task remained significant after co-varying for performance on the VOSP screening task (see Appendix 7.4.4 and 7.4.5).

3.4.4 Logistic Regression

The results of the logistic regression analysis showed that the Incomplete Letters task contributed independently to the presence of psychotic symptoms in AD. These results strengthen the finding of visuoperceptual deficits in those with psychotic symptoms, and suggest a potential use for this task as a cognitive marker of psychotic symptoms in AD. However, the present study was unable to determine the task's ability in predicting the onset of psychotic symptoms in AD, and future research using a longitudinal design should aim to address this. In contrast, performance on the RVP task did not contribute independently to the presence of psychotic symptoms (as shown by a non-significant effect of RVP when entered into the regression model with the Incomplete Letters task). Instead, the results indicate that visuoperceptual ability may have contributed to performance on the RVP test. It may be that sustained attention would have independently contributed to the presence of psychotic symptoms in AD if an auditory sustained attention task had been used in the current study. Future research could explore such a hypothesis using tests of auditory sustained attention from the Test of Everyday Attention (such as Elevator Counting and Lottery subtests).

3.4.5 Limitations

The present research is not without some limitations, including the possibility of type 1 errors owing to the number of statistical comparisons that were carried out. However, significant differences remained after using a Bonferroni adjusted alpha level and Fisher's LSD to correct for multiple pairwise comparisons.

Other limitations include not controlling for the potentially confounding effects of duration of illness or prescription of ChEI medication. The demographic screening assessment included duration of illness, however many subjects were unable to recall the length of time they had been experiencing memory difficulties. The duration of illness was therefore measured by the date at which the subject first presented to the memory clinic. This was deemed unreliable given that symptoms appear at different

stages of the illness. The lack of correlation with MMSE score confirmed this variable as unreliable, and it was therefore excluded from the analysis. Consequently, MMSE was used as a proxy measure of duration of illness, as cognitive decline increases during the course of the illness.

All subjects prescribed past or present psychotropic medication were excluded from the analysis, with the exception of those taking ChEIs. In the present study, all but 11 subjects were receiving cognitive enhancers (donepezil, galantamine, rivastigmine and/or memantine). In order to maximise sample size, and therefore increase the power of the analysis, all subjects were included. Given the similar distribution of those on and off medication in the two groups (off medication: $n = 4$ and $n = 7$ in non-psychotic and psychotic groups respectively), this is unlikely to have had a significant effect on the results of the study. Although the most stringent method of comparing the two groups would be to exclude patients who are prescribed cognitive enhancers from future studies of this type, this is neither feasible nor practical.

In the present study, the total N of 70 was categorised into two groups; Non-Psychotic and Psychotic. The sample size in each group was adequate to detect differences of 13.6% between these groups (see Chapter 2, Section 2.1.4), but not to detect differences between subgroups. Therefore, it is likely that a number of the subgroup statistical analyses were insufficiently powered to detect a statistically significant between-groups effect. A larger sample size with equal subjects in each subgroup would benefit future research into the neurocognitive profiles of specific psychotic subgroups.

Another limitation to the current research, and to other research in this field, is the challenge involved in diagnosing a delusion or hallucination in AD. Many delusions, such as those involving ideas of persecution, infidelity and abandonment, can be accurate interpretations of real events, and care must be taken to determine this. It is also difficult to distinguish certain delusions from simple forgetting, as it is common for patients to confabulate ideas to fill in the gaps missing from memory. Hallucinations can also be challenging to diagnose, especially those occurring upon falling asleep or awakening. In order to more accurately determine psychotic symptoms in AD, one should address the patient's response to reality testing, and the persistence or recurrence of the delusion over time. Other factors adding to the

difficulty in diagnosing psychosis in AD include the similarity of the symptoms to other psychiatric disorders (e.g. schizophrenia, schizoaffective disorder, delusional disorder and mood disorders with psychotic features), and their association with episodes of delirium and substance use (drugs of abuse and medications). Given the challenges involved in accurately diagnosing psychosis in AD, a set of diagnostic criteria have been proposed, which aim to identify the psychotic features of AD, while excluding psychotic syndromes caused by other factors (Jeste & Finkel 2000). The current sample met all the diagnostic criteria for psychosis in AD, except that which states that "symptoms must be severe enough to cause some disruption to the patient's and/or others' functioning". The delusions and hallucinations reported in the current study were predominantly mild, as D2/3 receptor availability had been previously shown to increase even with mild, transient delusions (Reeves et al., 2009). The beliefs described by the present sample caused little disruption to the subjects' functioning, and for this reason the term 'psychotic symptoms in AD', as opposed to 'psychosis in AD', has been used throughout the study.

In addition to the clinical challenges of diagnosing psychotic symptoms in AD, the current research relies on informant-rated responses on the NPI in order to assess the presence of psychotic symptoms. Although the NPI was administered to the carer/relative who had the most frequent contact with the patient, many informants were not living with the patient and therefore found it difficult to respond to questions regarding the frequency of psychotic symptoms, or when they last occurred. For this reason, all patients who had ever experienced a psychotic symptom were included in the analysis, in order to avoid excluding those currently experiencing occasional symptoms, which had gone unnoticed due to infrequent contact with the carer/informant. This also enabled a larger sample size to be included, adding to the reliability of the results. In order to ensure there were no significant state vs. trait effects of psychotic symptoms on the current results, a sensitivity analysis was carried out after excluding those who were no longer experiencing psychotic symptoms ($n = 6$). This made no difference to the present findings (see Appendix 7.4.2).

To make the present research more accessible for the elderly population, the neuropsychological test battery was administered in the home environment of the subjects. Although home visits help to maximise recruitment to the study, and can

reduce anxiety levels, they also lead to an increased amount of environmental disturbances during the assessment. Efforts were made to separate the subject and caregiver, in order to avoid them communicating during the testing procedure e.g. the subject asking their caregiver for help on certain questions. In addition, subjects were asked to turn off audio distractions such as the radio and TV, and to refrain from answering the phone/door during the assessment. However, disturbances inevitably occurred and the possibility that these distractions may have influenced cognitive performance cannot be ruled out.

3.5 Conclusion

The present study successfully addressed all four aims laid out in the introduction. Consistent with the original hypothesis is the finding of impaired sustained attention, as measured by the RVP, in subjects with psychotic symptoms in AD. However, motor speed did not differ between the two groups. When the neuropsychological profile of psychotic symptoms in AD was investigated across a range of cognitive domains, only visuo perceptual performance differed between the two groups, as measured by the Incomplete Letters task. Subgroup analysis of the significant between-group differences in neuropsychological test performance, in terms of paranoid (persecutory delusions) and misidentification (misidentification delusions and/or visual hallucinations) subtypes, demonstrated that the significant between-group differences observed in the RVP and Incomplete Letters tasks were driven predominantly by the misidentification subgroup. Logistic regression analysis showed an independent contribution of the Incomplete Letters task, but not RVP performance, to the presence of psychotic symptoms. The lack of independent contribution of the RVP to psychotic symptoms may be explained by the fact that visuo perceptual processing is a component of the RVP task, in addition to sustained attention. The implications of this will be discussed in Chapter 6, Section 6.3.1.

Chapter 4: Establishing the Test-Retest Reliability of an Adapted [¹⁸F]fallypride Imaging Protocol for Use in Older People

4.1 Introduction

Since dopamine D2/3 receptors were first visualised *in vivo* in man (Farde et al., 1986), PET tracers that target dopamine D2/3 receptors have provided important insights into the pathophysiology and treatment of psychiatric and neurological disorders. For example, D2/3 receptor tracers have increased our understanding of the human brain changes occurring in addiction, by consistently demonstrating decreased striatal D2/3 receptor availability in patients with a wide variety of drug addictions (Volkow et al., 2004; Volkow et al., 1999). Such tracers have also been used to investigate the mechanisms involved in the pharmacological treatment of ADHD (Volkow et al., 2001; Volkow et al., 2002). In addition, imaging of D2/3 receptors has generated important insights into the aetiology of schizophrenia, providing *in vivo* support for the ‘dopamine hypothesis’, which attributes dysregulation of dopaminergic transmission to be the cause of psychotic symptoms in schizophrenia (Laruelle & Abi-Dargham 1999). One of the most influential translational achievements of tracers which target D2/3 receptors, has been their role in guiding treatment strategies in schizophrenia, by establishing a ‘therapeutic window’ of striatal D2/3 receptor occupancy by antipsychotic drugs (Kapur 1998) - discussed in Chapter 1, Section 1.5.2.

4.1.1 Use of High Affinity Radiotracers to Image D2/3 Receptor Occupancy

More recently, the development of high affinity D2/3 receptor radiotracers, such as [¹⁸F]fallypride and [¹¹C]FLB-457, have enabled the clinical relevance of extrastriatal receptors to be explored, where the density of D2/3 receptors is 10-100 times lower than in the striatum (Kessler et al., 1993). A PET study using [¹¹C]FLB-457 demonstrated that temporal D2/3 receptors were a common target for both typical and atypical antipsychotics (Xiberas et al., 2001b). The same study also demonstrated a limbic selectivity of the atypical antipsychotics, whereby D2/3 occupancies were higher in the temporal cortex compared to the striatum. This was not the case with the

typical antipsychotics, which showed equally high occupancies in both regions. Occupancy studies using [¹⁸F]fallypride have also reported higher D2/3 receptor occupancy in temporal compared to striatal regions for several atypical antipsychotics (clozapine, quetiapine and aripiprazole) (Grunder et al., 2005; Kegeles et al., 2008; Kessler et al., 2005; Kessler et al., 2006). The limbic selectivity of atypical antipsychotics, demonstrated using PET imaging techniques, provides support to previous results from less sensitive SPECT studies, which showed relatively low striatal occupancies compared to occupancies in the temporal cortex e.g. 32 vs. 60.1% (quetiapine), 41.3 vs. 82.8% (olanzapine), and 58 vs. 90% (clozapine) (Bigliani et al., 2000; Pilowsky et al., 1997; Stephenson et al., 2000). Given the evidence that binding in the striatum is associated with EPS, and atypical antipsychotics have a lower tendency to induce these symptoms, temporal D2/3 receptor occupancy has been implicated in response, but not adverse effect, profiles of antipsychotic drugs (Stone et al., 2009). The hypothesis that high temporal occupancy, in conjunction with lower striatal occupancy, could result in a favourable response/side effect profile for an antipsychotic drug is supported by the antipsychotic clozapine. Clozapine blocks D2/3 receptors in the temporal cortex in excess of striatal receptors, and presents with high clinical efficacy and few EPS (Pilowsky et al., 1997). Since the development of the high affinity D2/3 radiotracers, the clinical relevance of the corticolimbic D2/3 receptors has become a fast growing area of research, which could potentially aid the development of novel antipsychotics with minimal adverse effects. However, although there is evidence that many atypical antipsychotics have higher D2/3 receptor occupancy in temporal compared to striatal regions, this is not a universal finding (discussed by Kessler et al., 2006), and further exploration of the clinical relevance of extrastriatal D2/3 receptors is needed.

4.1.2 Use of High Affinity Radiotracers to Image Endogenous Dopamine Release

In addition to receptor occupancy studies, high affinity D2/3 radiotracers are also used to image endogenous neurotransmitter release, and have enabled the role of corticolimbic dopamine release in human behaviour to be explored (Riccardi et al., 2006; Riccardi et al., 2011). Additionally, high affinity tracers have been used in a range of neurological and psychiatric illnesses including schizophrenia-spectrum

disorders (Woodward et al., 2011) and PD (Ray et al., 2012). Dopamine release during normal human behaviour was imaged for the first time in 1998, using [^{11}C]raclopride (Koepp et al., 1998). Since then, this phenomenon has been continually explored, with many refinements and improvements to the methodology in the past decade. Dopamine release studies are based on the ‘occupancy model’, which describes the competition between endogenous dopamine and radiotracer for the D2/3 receptor. An increase in the level of synaptic dopamine results in a decrease in tracer accumulation, and vice versa. Direct dopamine-enhancing challenges, such as amphetamine, have been used in both primates (Dewey et al., 1993; Laruelle et al., 1997) and humans (Abi-Dargham et al., 1998; Kegeles et al., 1999; Laruelle et al., 1996; Laruelle et al., 1995; Volkow et al., 1994), to demonstrate the decrease in radiotracer binding. The magnitude of changes in BP reported using the occupancy model correlate with the magnitude of changes in dopamine level measured with microdialysis, supporting the use of non-invasive techniques to measure dopamine neurotransmission (Breier et al., 1997; Laruelle et al., 1997). Dopamine release studies are an important area of research, from which we can investigate the dopaminergic basis of human behaviour and its role in disease mechanisms.

4.1.3 [^{18}F]fallypride Imaging: Advantages and Limitations

[^{18}F]fallypride is unique amongst D2/3 receptor tracers, as it can provide stable estimates of both striatal and extrastriatal receptor availability within the same scanning session (Mukherjee et al., 2002). In contrast, the short half-life of carbon-11 (20 minutes) limits the use of [^{11}C]FLB-457 to imaging extrastriatal regions only, due to the length of time needed to reach a plateau of binding in the striatum, where receptor density is high. However, despite the advantages of [^{18}F]fallypride, the techniques currently used to quantify D2/3 receptor binding involve multiple sampling periods (each lasting 60-70 minutes) over a total scan duration of 3-4 hours. This is to allow tracer uptake to achieve a plateau within the striatum, where D2/3 receptors are most densely concentrated (Mukherjee et al., 2002). These imaging protocols are not feasible for use in many clinical populations, particularly older, cognitively impaired individuals, or those with movement disorders. Previous experience of conducting imaging studies in older people (Reeves et al., 2009; Reeves et al., 2005) has shown

that scanning sessions longer than 60 minutes are difficult to tolerate, particularly in those with cognitive impairment. Suggested reasons as to why longer scans are not tolerable include: joint pain, low temperatures in the scanning room, disruption to daily routines (e.g. meal times), anxiety due to an unfamiliar environment, and confusion due to memory deficits causing patients to forget where they are and for what purpose. Adapting [^{18}F]fallypride imaging for use in clinical populations who are unable to tolerate lengthy scanning sessions would widen its potential for use in understanding disease mechanisms, drug occupancy, and dopamine release in response to pharmacological and behavioural challenge.

4.1.4 Adapting [^{18}F]fallypride Imaging

The current study has devised an adapted [^{18}F]fallypride scanning protocol, which minimises the time spent in the scanner. The timings of the current protocol were based upon pilot data using [^{18}F]fallypride in young adults, and on studies which have previously used [^{18}F]fallypride to measure D2/3 receptor occupancy in young adults with schizophrenia (Kegeles et al., 2008; Kessler et al., 2006). The protocol was designed to capture peak binding, with particular emphasis placed on avoiding capturing pre-equilibrium binding, which can lead to errors in the estimation of BP_{ND} . The scanning times of the adapted protocol are: 0-30 minutes, to provide an input function to model a reference region approach; 60-90 minutes, to measure the peak tracer binding within extrastriatal regions; and 210-240 minutes, to ensure that tracer binding has achieved a plateau in the striatum of all subjects. The current study allows us to investigate the effect of shorter scan durations rather than total uptake time, which has been increased to ensure equilibrium is reached in all striatal regions (in a small proportion of people, tracer may take up to 210 minutes to achieve equilibrium (Vernaleken et al., 2011)).

4.1.5 Aims

The broad aims of the study were to adapt [^{18}F]fallypride imaging for use in the elderly population, and to optimise the technique for use in D2/3 receptor occupancy studies in patients with AD. The specific aims of the study were as follows:

- (i) To establish the test-retest reliability (in healthy older adults) of an adapted [^{18}F]fallypride imaging protocol, which has reduced the length of individual scanning sessions to 30 minutes.
- (ii) To investigate whether sampling times could be further reduced to 20 minute sessions without reducing reliability.

4.2 Methods

A brief overview of the recruitment/screening procedure and the methodology involved in PET imaging is given in Chapter 2 (Sections 2.4 and 2.5). For the purposes of this study, the BP_{ND} is reported for the region of interest across both hemispheres, consistent with previous test-retest studies (Cropley et al., 2008; Mukherjee et al., 2002).

4.2.1 Scanning Protocol

The adapted scanning protocol is detailed in Chapter 2, Section 2.5.3, and consists of three scanning sessions: 0-30 minutes, 60-90 minutes, and 210-240 minutes. The initial 3 minutes of the first scanning session acquired frames with short duration (1 x 10 seconds, 10 x 5 seconds, 6 x 10 seconds, and 3 x 20 seconds). The remaining 87 minutes of scanning were acquired using frame lengths of 1 minute.

4.2.2 Optimising the Protocol

In order to establish whether sampling times could be further reduced to 20 minute sessions without reducing the reliability of the protocol, two sets of analyses were performed. Data were first analysed using the complete data set from three scanning sessions of 30 minutes, and then were reanalysed using only 20 minutes of data from

each scanning session. The two sets of analyses are referred to as Method 1: 0-30, 60-90 and 210-240 minutes; and Method 2: 0-20, 70-90 and 220-240 minutes.

4.2.3 Defining ROIs

The cerebellar reference region was defined using the Automated Anatomical Labelling Atlas (Tzourio-Mazoyer et al., 2002), and the Tziortzi Atlas (Tziortzi et al., 2011) was used to define the caudate, putamen and extrastriatal regions (thalamus, amygdala, hippocampus, middle and inferior temporal gyri, orbitofrontal cortex and anterior cingulate cortex). These regions were chosen to allow comparison with previous test-retest studies using [¹⁸F]fallypride (Cropley et al., 2008; Mukherjee et al., 2002). The striatal subdivisions were defined using a template which was originally defined using the same anatomical landmarks as Mawlawi et al. (2001), described in Chapter 2, Section 2.7.4.

4.2.4 Statistics

A paired t-test was used to compare the administered dose of [¹⁸F]fallypride between test and retest scans. The ICC (Fisher 1958) was calculated to measure the reliability of the test-retest BP_{ND} values for each region of interest. The absolute variability of test-retest reproducibility was calculated as follows: $[|test - retest| / ((test + retest) / 2)] \times 100$. The variability between mean BP_{ND} values for Methods 1 and 2 was determined by: $(|Method1_test - Method2_test| / Method1_test) \times 100$ and expressed as the mean and standard deviation (SD) across subjects. The coefficient of variation (COV) was calculated for each subject's BP_{ND} for the individual ROIs, and is presented as the mean % across subjects. 'PS' software was used to perform power calculations (Dupont & Plummer 1990). The regional percentage change in [¹⁸F]fallypride BP_{ND} detectable in a typical within-subjects comparison (sample size = 15; paired t-test) was calculated using a probability (power) of 0.8, and an associated type I error probability (α) of 0.05. Percentage variability in mean BP_{ND} was used as an estimate of within-subject SD.

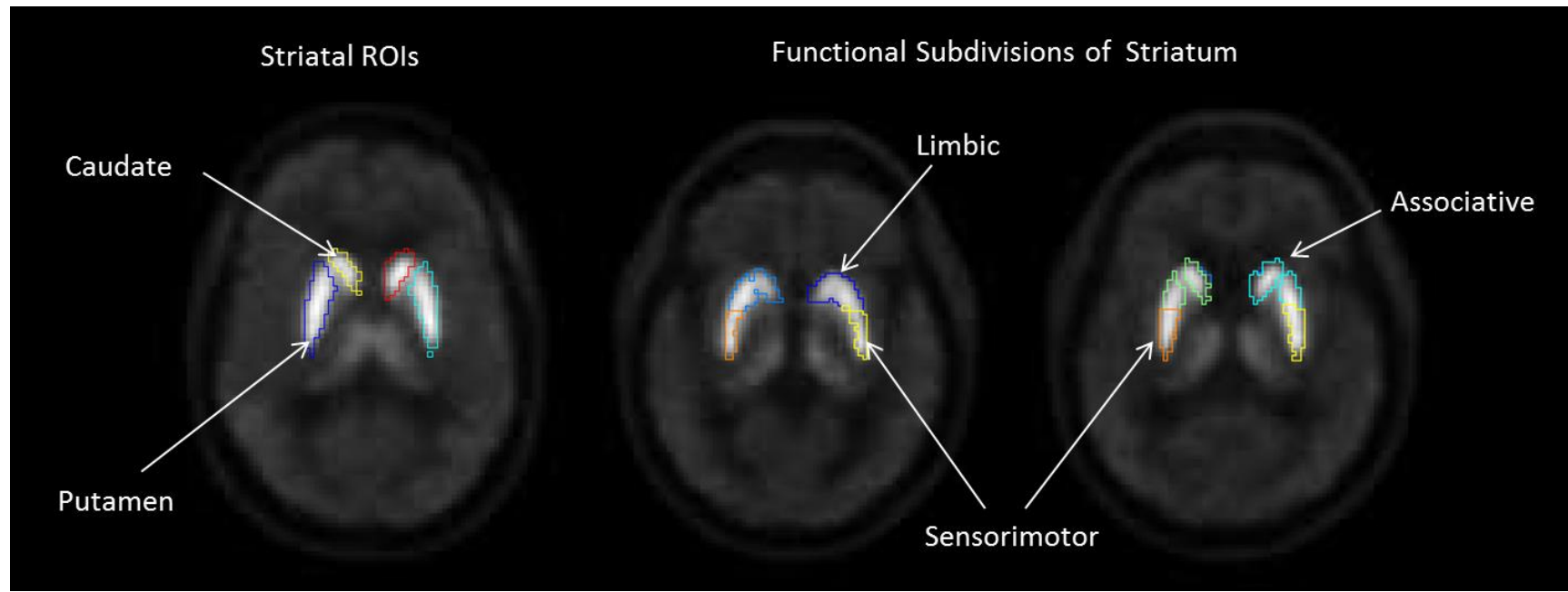
4.3 Results

Administered dose of [¹⁸F]fallypride was 244.1 ± 7.3 MBq. There were no significant differences in administered dose between test and retest scans (mean difference = 0.5 ± 10.8 MBq, $p = 0.90$).

4.3.1 Mapping of PET images to ROI

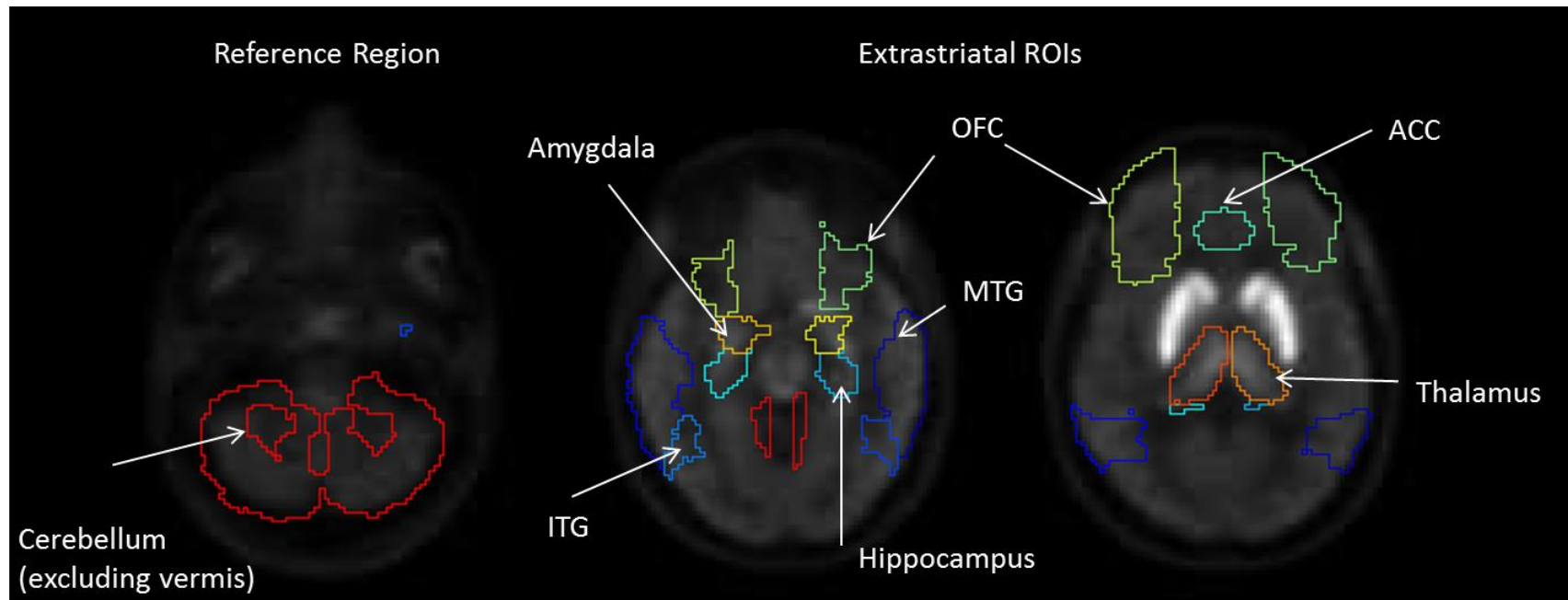
Figures 4.1 and 4.2 show the accuracy with which the ROIs were mapped onto an individual's PET scan, by warping the atlas via a [¹⁸F]fallypride template. The alignment of the ROIs with the individual's PET scan shows good accuracy in the striatal regions, using both anatomical and functional subdivisions. The alignment of the extrastriatal ROIs is also generally accurate, although not optimal in the orbitofrontal cortex.

Figure 4.1: Alignment of Striatal ROIs with an Individual's PET Scan



Striatal ROIs, defined using the Tziortzi Atlas (far left) and the functional subdivisions template, have been superimposed upon a [^{18}F]fallypride image in standard MNI space. All images show transverse view.

Figure 4.2: Alignment of Extrastriatal ROIs with an Individual's PET Scan



The reference region and extrastriatal ROIs, defined using the Anatomic Labelling Atlas and Tziortzi Atlas respectively, have been superimposed upon a [^{18}F]fallypride image in standard MNI space. All images show transverse view. ITG = inferior temporal gyrus, MTG = middle temporal gyrus, OFC = orbitofrontal cortex, ACC = anterior cingulate cortex.

4.3.2 Regional Uptake of [^{18}F]fallypride

Time-activity curves for Method 1 (30 minute sampling times) are shown in Figures 4.3-4.5 and represent the attenuation corrected (AC) filtered back projected (FBP) data on which the kinetic analysis was carried out. The curves show regions with high receptor concentration (caudate, putamen and striatal subdivisions), medium receptor concentration (amygdala and thalamus) and lower receptor concentration (hippocampus, temporal cortex, and frontal regions). Uptake in the striatal regions reached equilibrium at the start of the final scanning session (210-240 minutes), confirming that complete uptake of [^{18}F]fallypride was achieved. The extrastriatal regions reached a plateau of binding prior to the final scanning session. The general uptake pattern of [^{18}F]fallypride across the regions is similar to that of previous studies (Cropley et al., 2008; Mukherjee et al., 2002).

Figure 4.3: Time-Activity Curves (Method 1) Representing [^{18}F]fallypride Uptake in All ROIs in a Single Subject

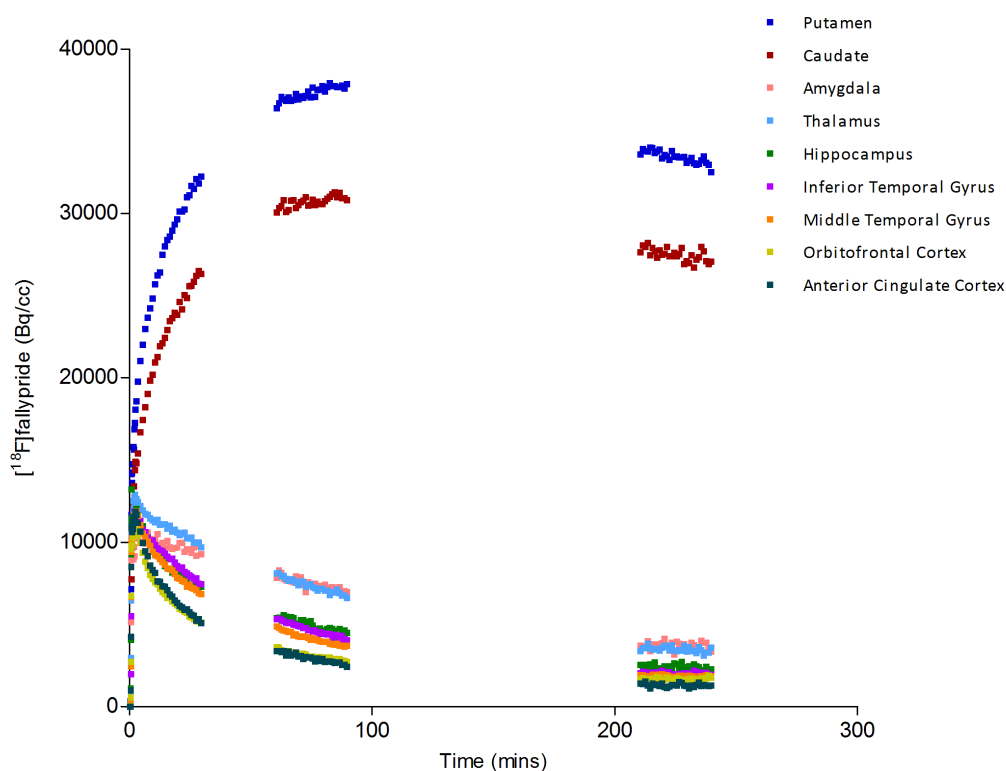


Figure 4.4: Time-Activity Curves (Method 1) Representing [^{18}F]fallypride Uptake in Striatal Subdivisions in a Single Subject

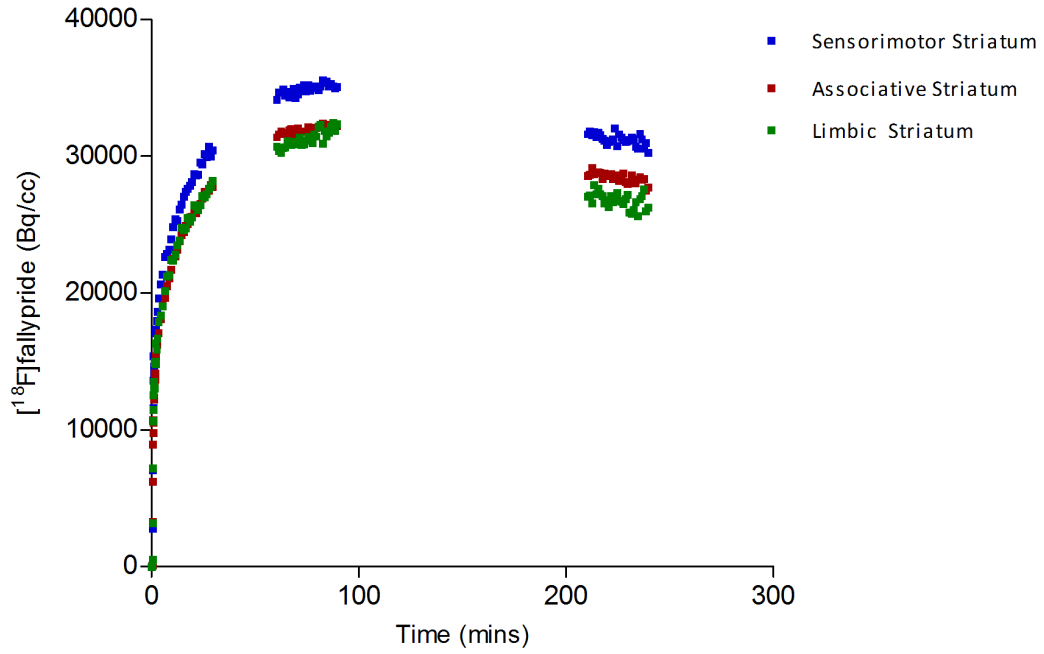
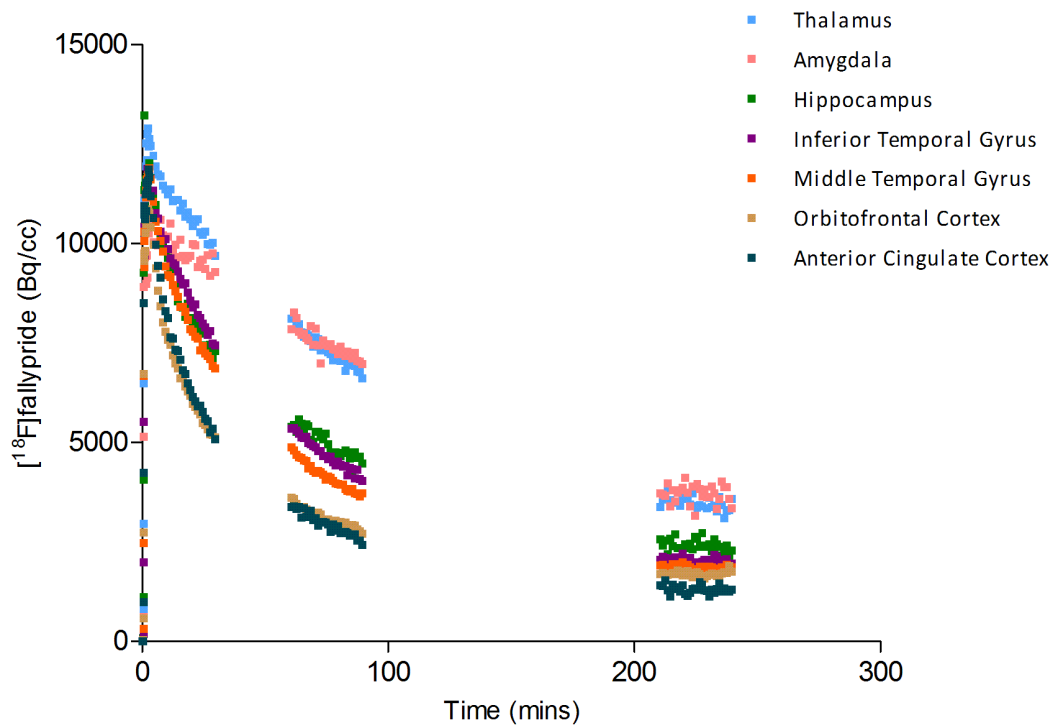


Figure 4.5: Time-Activity Curves (Method 1) Representing [^{18}F]fallypride Uptake in Extrastriatal ROIs in a Single Subject



4.3.3 Test-Retest Reproducibility of Regional [¹⁸F]fallypride Binding

Method 1

Test-retest variability and ICC values of regional [¹⁸F]fallypride binding for Method 1 are presented in Table 4.1. All regions examined showed high reproducibility (<8% variability), with the exception of the orbitofrontal cortex (15.04% variability) and the anterior cingulate cortex (28.84% variability). The highest reproducibility was seen in the caudate, putamen, amygdala, and inferior temporal gyrus (<5% variability). The reliability was high in all regions, ranging from 0.80 in the limbic striatum to 0.99 in the middle and inferior temporal gyri.

Method 2

Mean percentage test-retest differences (% variability) and reliability (ICC) of regional [¹⁸F]fallypride binding for Method 2 (20 minute sampling times) are presented in Table 4.2. Reproducibility remained high (<8% variability) in all regions, with the exception of the limbic striatum (8.25%), and the prefrontal regions (orbitofrontal cortex = 17.45%; anterior cingulate cortex = 37.35%). In line with Method 1, the highest reproducibility was seen in the caudate, putamen, amygdala and inferior temporal gyrus (<5.68%). The reliability remained high (>0.80) in all regions, apart from the anterior cingulate cortex (0.79). The greatest reliability (0.99) was seen in the middle and inferior temporal gyri.

Comparison of Method 1 and 2

The mean percentage difference between the BP_{ND} values derived from Method 1 compared to Method 2 was less than 2% in the striatal regions, amygdala, thalamus and hippocampus. The percentage difference between methods was <3.19% in the remaining regions, with the exception of the anterior cingulate cortex, which showed a difference of 14.47% between methods (Table 4.2).

Table 4.1: Test-Retest Reproducibility of Regional [¹⁸F]fallypride Binding Using Method 1 (3 x 30 minute scanning sessions)

Region	Test¹	Retest¹	Variability %²	ICC³
Sensorimotor striatum	19.73 (2.66)	19.70 (2.06)	5.56 (2.69)	0.86
Associative striatum	17.50 (2.39)	17.58 (1.77)	5.05 (5.33)	0.85
Limbic striatum	16.90 (2.83)	17.04 (2.00)	7.12 (7.37)	0.80
Putamen	21.19 (2.82)	21.50 (2.15)	4.99 (3.76)	0.88
Caudate	16.57 (2.77)	16.71 (2.29)	3.44 (3.87)	0.96
Amygdala	1.77 (0.41)	1.76 (0.38)	4.08 (4.64)	0.98
Thalamus	1.48 (0.28)	1.47 (0.24)	6.10 (6.70)	0.90
Hippocampus	0.82 (0.21)	0.79 (0.19)	7.35 (6.40)	0.95
Inferior temporal gyrus	0.57 (0.21)	0.58 (0.20)	4.83 (7.61)	0.99
Middle temporal gyrus	0.39 (0.17)	0.39 (0.17)	6.40 (9.45)	0.99
Orbitofrontal cortex	0.21 (0.10)	0.23 (0.11)	15.04 (15.68)	0.92
Anterior cingulate cortex	0.18 (0.10)	0.18 (0.09)	28.84 (39.59)	0.82

¹BP_{ND} given as mean across subjects (SD); ²Absolute variance given as mean across subjects (SD) = [(test-retest)/(test+retest)/2] * 100; ³Intraclass Correlation Coefficient.

Table 4.2: Test-Retest Reproducibility of Regional [¹⁸F]fallypride Binding Using Method 2 (3 x 20 minute scanning sessions)

Region	Test ¹	Retest ¹	Variability % ²	ICC ³	Method 1 Vs. Method 2 ⁴
Sensorimotor striatum	19.82 (3.04)	19.70 (2.06)	6.37 (3.70)	0.84	1.77 (1.13)
Associative striatum	17.55 (2.64)	17.56 (1.84)	5.80 (5.91)	0.84	1.66 (0.93)
Limbic striatum	16.94 (3.06)	16.99 (2.06)	8.25 (6.97)	0.80	1.56 (0.89)
Putamen	21.27 (3.19)	21.49 (2.21)	5.68 (4.86)	0.86	1.69 (0.98)
Caudate	16.62 (3.06)	16.68 (2.35)	4.43 (4.43)	0.95	1.72 (0.90)
Amygdala	1.76 (0.42)	1.75 (0.38)	4.70 (5.30)	0.97	1.02 (0.74)
Thalamus	1.47 (0.29)	1.46 (0.23)	6.60 (7.25)	0.89	1.13 (0.74)
Hippocampus	0.81 (0.21)	0.79 (0.18)	7.67 (7.84)	0.94	1.38 (1.11)
Inferior temporal gyrus	0.56 (0.21)	0.57 (0.20)	5.28 (9.96)	0.99	2.89 (2.60)
Middle temporal gyrus	0.38 (0.18)	0.38 (0.17)	7.94 (10.47)	0.99	3.19 (2.76)
Orbitofrontal cortex	0.21 (0.10)	0.22 (0.11)	17.45 (14.23)	0.92	2.70 (2.41)
Anterior cingulate cortex	0.17 (0.11)	0.17 (0.09)	37.35 (54.16)	0.79	14.47 (20.50)

¹BP_{ND} given as mean across subjects (SD); ²Absolute variance given as mean across subjects (SD) = [(test-retest)/(test+retest)/2]*100; ³Intraclass Correlation Coefficient; ⁴Given as mean percentage difference between Method 1 and Method 2 test BP_{ND} (SD) = (|Method1_test-Method2_test/Method1_test)*100.

4.3.4 Reliability of Individual BP_{ND} Values

Coefficient of Variation

The COV was calculated for each subject's BP_{ND} across the individual ROIs, and is presented in Table 4.3 as the mean % across subjects. The individual BP_{ND} values showed high reliability, with the COV less than 1% in both test and retest scans for Methods 1 and 2, in all regions apart from the hippocampus, temporal cortex and frontal regions. Using Method 1, the COV was <3% in the remaining regions, with the exception of the anterior cingulate cortex, which was 9.07% and 6.38% for the test and retest scans respectively. Using Method 2, the COV was slightly higher, at <4% in the remaining regions apart from the anterior cingulate cortex, which was 20.47% and 8.44% for the test and retest scans.

Table 4.3: Mean COV Across Subjects for Individual ROIs

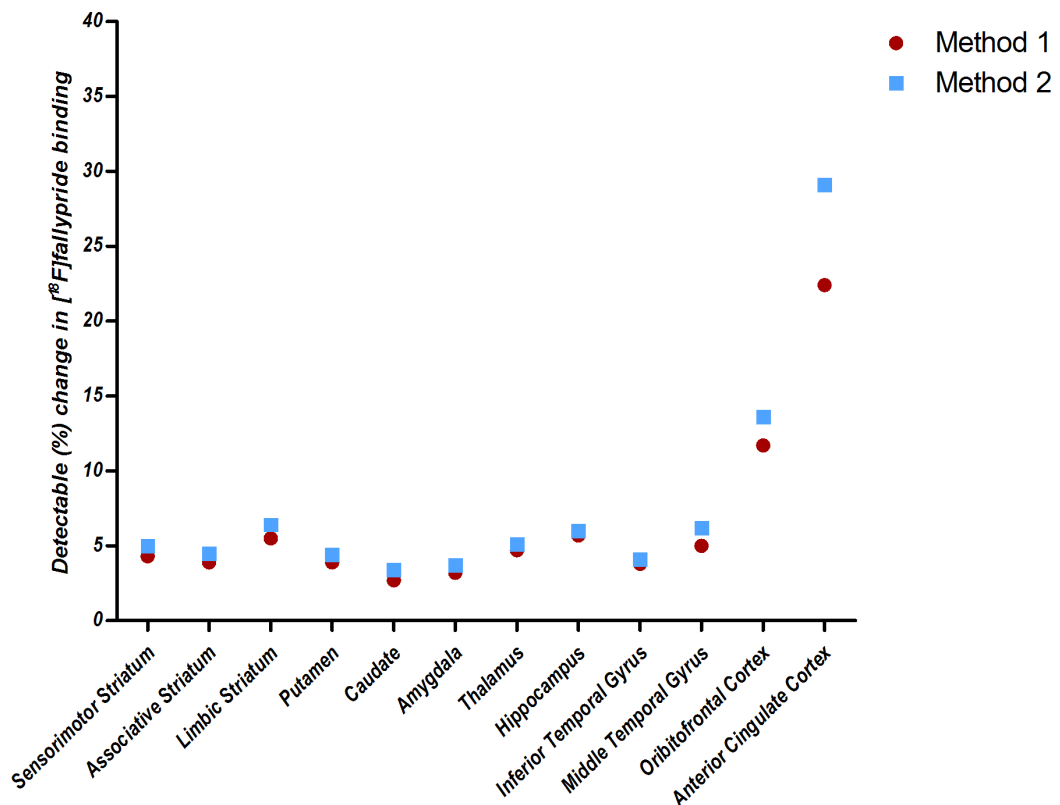
Region	COV % Method 1		COV % Method 2	
	Test	Retest	Test	Retest
Sensorimotor striatum	0.51	0.56	0.70	0.76
Associative striatum	0.50	0.50	0.69	0.68
Limbic striatum	0.56	0.55	0.75	0.71
Putamen	0.45	0.49	0.63	0.68
Caudate	0.44	0.49	0.62	0.67
Thalamus	0.63	0.50	0.80	0.62
Amygdala	0.86	0.82	1.09	1.02
Hippocampus	1.18	1.11	1.47	1.38
Inferior temporal gyrus	2.03	1.78	2.52	2.15
Middle temporal gyrus	2.54	2.30	3.12	2.81
Orbitofrontal cortex	2.43	2.71	3.09	3.36
Anterior cingulate cortex	9.07	6.38	20.47	8.44

4.3.5 Regional Detectable Within-Subject % Change in [¹⁸F]fallypride Binding

The results of a power analysis for a within-subject study design (N = 15, paired t-test; $\alpha = 0.05$, power = 0.8) are shown in Figure 4.6. The standard sample size of 15 was chosen based on previous studies which have included samples of 10-25 subjects (Narendran et al., 2009; Ray et al., 2012; Riccardi et al., 2006; Riccardi et

al., 2011; Slifstein et al., 2010). The results indicate that with an N of 15, Method 1 would be sufficiently sensitive to detect changes of 5% or less in all regions apart from the limbic striatum (5.5%), hippocampus (5.7%), orbitofrontal cortex (11.7%) and anterior cingulate cortex (22.4%). Method 2 is marginally less sensitive to changes in [¹⁸F]fallypride binding, detecting changes of 5% or less across fewer regions than Method 1 (caudate, putamen, dorsal striatal subdivisions, inferior temporal gyrus and amygdala), and larger changes in the other regions; <6.5% in the limbic striatum, hippocampus and inferior temporal gyrus, and 13.6% and 29.1% in the orbitofrontal cortex and anterior cingulate cortex respectively. The lower sensitivity of Method 2 is emphasised in the frontal regions. Figure 4.6 shows the current protocol is most sensitive to detecting percentage changes in [¹⁸F]fallypride binding in the caudate, and least sensitive to detecting changes in the frontal regions (orbitofrontal cortex and anterior cingulate cortex).

Figure 4.6: Regional Detectable % Change in [¹⁸F]fallypride Binding Using Method 1 and Method 2



4.4 Discussion

This study has shown high reproducibility of an adapted [^{18}F]fallypride protocol across the striatum, consistent with previous test-retest studies using [^{18}F]fallypride in young adults, which have used full modelling with arterial sampling (Mukherjee et al., 2002) or a simplified reference tissue approach (Cropley et al., 2008) to image analysis. High reproducibility (<8% variance) was also seen in the majority of extrastriatal regions; however not in the prefrontal regions, in particular the anterior cingulate cortex, where BP_{ND} differed by 28.84% between test and retest. These findings are consistent but more marked than those of Cropley et al. (2008) who similarly reported a high variability in the anterior cingulate cortex ($21.8 \pm 3.8\%$) in healthy young adults. One reason for the increased variability in the frontal regions may be due to a relatively low signal to noise ratio of [^{18}F]fallypride in this region, given the low D2 receptor density identified in these regions post mortem (Kessler et al., 1993).

The second aim of this study was to identify whether sampling times could be further reduced to 20 minute sessions without affecting reliability. The present results show that individual scanning sessions of 20 minutes produced the same pattern of reproducibility across striatal and extrastriatal regions as the original 30 minute protocol. The test-retest variability increased minimally (<3.2%) in all regions except the anterior cingulate cortex, where the increase was more substantial (14.47%).

In order to establish the reliability of the individual BP_{ND} values in the current study, the COV across subjects was calculated, demonstrating high reliability in all striatal regions (<1% variance) and extrastriatal regions (<3.36% variance) bar the anterior cingulate cortex. The high variance observed in the individual BP_{ND} values in the anterior cingulate cortex may have contributed to the poor test-retest reliability in this region.

4.4.1 Consideration of Age-Related Factors in D2/3 PET Imaging

Several studies have reported a decline in D2 receptor binding with age in both striatal (reviewed by Reeves et al., 2002) and extrastriatal regions (Inoue et al., 2001; Kaasinen et al., 2000). The absolute BP_{ND} values in the caudate (16.57) and putamen

(21.19) reported in the current study are consistent with the eldest subject (aged 63 years) in a previous [¹⁸F]fallypride test-retest study (caudate = 15.6, putamen = 19.3), however are considerably lower than those reported in the youngest subject (aged 21 years) in the same study (caudate = 31.4, putamen = 36.3) (Mukherjee et al., 2002). This is consistent with studies which report a decrease in D2 receptor density in the caudate between 4.5% and 7.5% per decade (Rinne 1987; Rinne et al., 1990; Severson et al., 1982), with similar reductions reported in the putamen (De Keyser et al., 1990; Morgan et al., 1987; Severson et al., 1982). Most relevant to the current finding of increased variability in the anterior cingulate and orbitofrontal cortices is the faster rate of D2/3 receptor decline seen in the frontal regions (Inoue et al., 2001). This is particularly prominent in the anterior cingulate cortex, where the D2/3 receptor density is reported to decline at a rate of 13% per decade, in contrast to 5% per decade in the thalamus (Kaasinen et al., 2000). This is consistent with Mukherjee et al. (2002) who reported the greatest decrease in binding per decade to occur in the frontal regions (15-20%). Such low receptor densities could result in a relatively low signal to noise ratio of [¹⁸F]fallypride in the frontal regions, therefore accounting for the poor reproducibility in these regions.

In addition to age-related decreases in D2/3 receptor density, age-related volume loss has also been demonstrated by MRI studies, and is especially prominent in the frontal lobes (Coffey 1993; Cowell et al., 1994; Raz et al., 1997; Salat et al., 1999; Tisserand et al., 2002). Few studies have considered the different substructures within the prefrontal cortex, however two out of the three studies that have addressed this found the strongest age-associated volume loss to be in the anterior cingulate cortex, with the orbitofrontal cortex remaining fairly preserved (Salat et al., 1999; Tisserand et al., 2002). The liability of the anterior cingulate cortex to age-related volume loss could help to explain the poor reproducibility in this region; possibly due to enhanced partial volume effects (see Chapter 6, Section 6.2.3).

4.4.2 Suitability for Occupancy Studies

The primary aim of the current study was to adapt [¹⁸F]fallypride imaging to minimise the length of individual scanning sessions. The current protocol has achieved this, showing high reliability and reproducibility, in agreement with other

[¹⁸F]fallypride studies (Cropley et al., 2008; Mukherjee et al., 2002). The shortened scan durations enhance the feasibility and accessibility of [¹⁸F]fallypride imaging for use across a range of neuropsychiatric disorders in which dopamine has been implicated, including patients with dementia, PD, movement disorders and disorders of impulsivity. Our main area of interest is to develop a scanning protocol suitable for use in D2/3 receptor occupancy studies in older and/or cognitively impaired patients. The current protocol is sufficiently sensitive to detect small percentage changes in all but the prefrontal regions, and therefore can be utilised to investigate the role of cortical vs. striatal D2/3 occupancy in response to antipsychotic treatment. Despite the urgent clinical need to optimise dosing regimens of antipsychotic medications in the elderly, this area of research has been largely neglected. The high reproducibility of the adapted [¹⁸F]fallypride imaging protocol suggests it is a reliable method for measuring D2/3 receptor occupancy in older adults, and the next stage of the research will be to optimise the protocol for use in patients with AD, following antipsychotic medication (Chapter 5).

4.4.3 Suitability for Dopamine Release Studies

In addition to receptor occupancy studies, the current study aimed to establish the sensitivity of the protocol to detect changes in endogenous dopamine following pharmacological or behavioural intervention. The past decade has demonstrated [¹⁸F]fallypride PET imaging to be a suitable method of measuring endogenous dopamine release in the striatum, using amphetamine displacement studies in both animals (Mukherjee et al., 1997; Slifstein et al., 2004) and humans (Cropley et al., 2008; Riccardi et al., 2006). The same studies have also demonstrated a sufficiently robust effect across limbic (hippocampal, amygdala) regions.

In contrast, the suitability of [¹⁸F]fallypride to measure changes in other cortical regions, in particular the frontal regions, is less well established. A finding of no significant change in [¹⁸F]fallypride binding in response to amphetamine in the frontal regions (dorsolateral prefrontal cortex, orbitofrontal cortex and medial orbitofrontal cortex), together with low baseline BP_{ND} values and high variability between baseline and post-challenge scans, led authors to conclude that [¹⁸F]fallypride is not a suitable tool for reliably measuring dopamine release in the

frontal regions (Slifstein et al., 2010). Support for this conclusion is provided by another study, which directly compared [^{18}F]fallypride and [^{11}C]FLB-457 in terms of their ability to measure dopamine release in cortical regions in response to amphetamine. This study reported a significant effect of amphetamine in the cortex using [^{11}C]FLB-457, but not [^{18}F]fallypride (Narendran et al., 2009). Although, Cropley et al. (2008) reported a significant decrease in [^{18}F]fallypride binding in the medial orbitofrontal cortex, the remaining frontal regions, including the anterior cingulate cortex, were not evaluated. This could again be due to the relatively low baseline BP_{ND} (< 0.5) and high variability of BP_{ND} (21.8%) between test and retest scans.

Previous studies report mean displacements of [^{18}F]fallypride between 5-16% in the striatal regions, and 4.4-15% in limbic regions (Cropley et al., 2008; Narendran et al., 2009; Riccardi et al., 2008; Riccardi et al., 2006; Slifstein et al., 2010). The power calculations carried out on the current results, using a standard sample size of 15, indicates that Method 1 will be sufficiently sensitive to detect within-subject changes across the striatal and limbic regions, ranging from 2.7% in the caudate to 5.7% in the hippocampus. Method 2 is slightly less sensitive, with detectable differences ranging from 3.4% in the caudate to 6.4% in the limbic striatum. Neither method is sufficiently sensitive to measure endogenous dopamine release in the frontal regions, consistent with previous literature mentioned above.

The high sensitivity of the adapted [^{18}F]fallypride imaging protocol supports its use in a two scan approach to detect minute differences in dopamine release in striatal and limbic regions. The shorter scanning times involved make dopamine release studies more feasible and accessible to a wider clinical population. It is not yet established whether these findings will generalise to cognitively or neurologically impaired populations, however given the fact that sensitivity to detect within-subject change is crucial for studies of this type, it may be advisable to collect data over the longer (30 minute) sampling times used in the original protocol, and to obtain a suitably large sample size.

4.4.4 Potential Limitations

MRI and Partial Volume Effects

In an attempt to increase the tolerability of the protocol, the current study did not use MRI data for co-registration with PET data. The templates used for co-registration originated from structural and functional imaging data on healthy young adults and this may have impacted upon the warping process. Visual inspection of the accuracy with which the ROIs aligned with individuals' PET scans did not show any substantial misalignments, although small inaccuracies in the alignment of the orbitofrontal cortex may have contributed to the higher variability in this region (see Figure 4.2). In addition, partial volume effects, which are particularly relevant in older adults (Morris et al., 1999), are also likely to have affected the accuracy of tracer quantification in the current study. These factors are discussed in further detail in Chapter 6, Section 6.2.3.

Sampling Times

The sampling times used in the current study to quantify cortical and striatal BP_{ND} were based upon [^{18}F]fallypride studies carried out in young adults (see Chapter 2, Section 2.5.3). The accuracy with which these timings are able to capture peak tracer binding in the elderly population is worth considering, given that the time taken to achieve peak tracer binding is dependent upon receptor density, and may be affected by age-related factors including peripheral clearance, regional cerebral blood flow and BBB transport. The possibility that the adapted protocol did not optimally capture peak tracer binding in all subjects can therefore not be excluded. Another consideration, given the lower density of D2/3 receptors in extrastriatal regions, is that equilibrium will have been achieved considerably earlier than the 240 minutes needed to achieve equilibrium in the striatum. The increased sampling time of 240 minutes may have added unnecessary noise to the data, contributing to the high variability seen in the anterior cingulate cortex. However, given the fact that our findings are in line with previous test-retest data (Cropley et al., 2008), the low signal to noise ratio in the anterior cingulate cortex, combined with age-associated D2/3 receptor loss in this region, is likely to explain the findings without further exploring the modelling assumptions.

4.5 Conclusion

We have successfully adapted [¹⁸F]fallypride imaging using an interrupted scanning protocol which considerably shortens the time spent in the scanner. The high reproducibility and reliability of the adapted protocol means that it can be applied not only to D2/3 receptor occupancy studies, but also to image endogenous neurotransmission in striatal and limbic regions. The shorter scanning times required in the adapted [¹⁸F]fallypride protocol could help to advance research across a range of cognitively and neurologically impaired populations in which dopamine has been implicated.

Chapter 5: Optimising [¹⁸F]fallypride Imaging for D2/3 Occupancy Studies in AD

5.1 Introduction

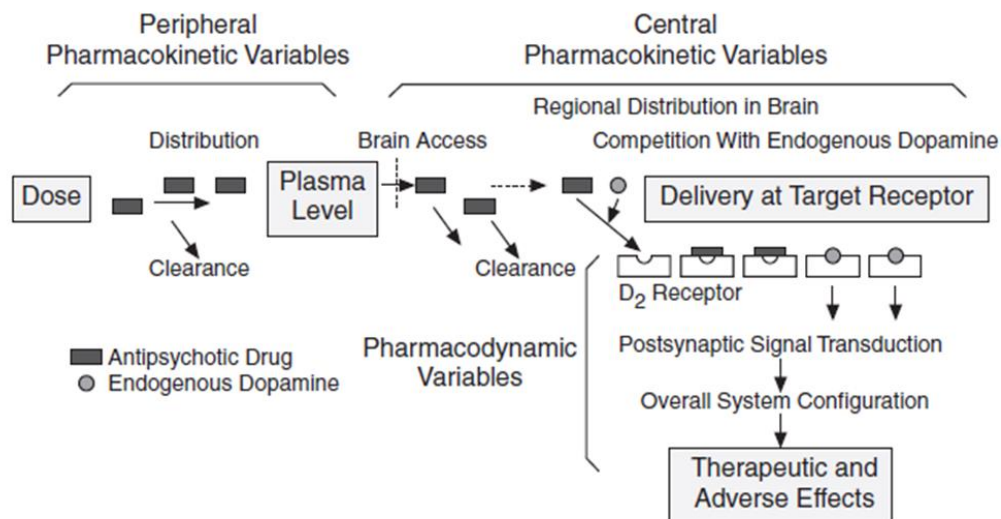
A major translational achievement of PET neuroreceptor imaging has been its role in guiding and informing treatment strategies in schizophrenia, by establishing a ‘therapeutic window’ of striatal D2/3 receptor occupancy by antipsychotic drugs. A threshold of 60-80% occupancy is required for therapeutic response, whereas occupancy above this increases the risk of developing EPS (Kapur 1998) (discussed in Chapter 1, Section 1.5.2). This research has been instrumental in guiding treatment strategies of schizophrenia in young adults. The ‘therapeutic window’ has also been used to guide the development and evaluation of new antipsychotics (de Greef et al., 2011). However, in contrast to the abundance of data on young adults, this area of research has been relatively neglected in older adults, particularly those with dementia, who are most vulnerable to antipsychotic treatment, and could potentially benefit most from the clinical application of imaging techniques. It is suggested that the limited research in this population may be due to the lengthy scanning times involved in imaging procedures. Chapter 4 describes an adapted imaging protocol, which minimises the time spent in the scanner, and could be the first step towards increasing research into the mechanisms of antipsychotic sensitivity in AD, and establishing a ‘therapeutic window’ of occupancy. The current chapter aims to further adapt the protocol for use in D2/3 receptor occupancy studies in the AD population.

5.1.1 Antipsychotic Sensitivity in the Elderly: Mechanisms

Antipsychotic drugs are used to treat behavioural (agitation/aggression) and psychotic (delusions/hallucinations) symptoms in AD, both of which are common causes of patient and carer distress, and have been associated with earlier institutionalisation (Steele et al., 1990). Current prescribing of antipsychotics in AD is associated with a high rate of side effects including: EPS, sedation, postural hypotension, falls, and increased mortality due to cerebrovascular events (Ballard &

Howard 2006). There is therefore an urgent clinical need to determine the underlying cause of such heightened sensitivity, in order to improve treatment, reduce morbidity, and improve quality of life. However, despite the need to understand the reasons for such sensitivity to the drugs, research in this field is sparse. The following theories have been proposed by one research group: (i) The peripheral pharmacokinetic hypothesis, (ii) The central pharmacokinetic hypothesis, and (iii) The pharmacodynamic hypothesis (Uchida et al., 2009b). Each of these theories relates to a different aspect of the drug pathway, from the injected dose to alterations at the target site (illustrated in Figure 5.1).

Figure 5.1: Proposed Mechanisms of Antipsychotic Sensitivity



(Uchida et al., 2009b)

Peripheral Pharmacokinetic Theory

The peripheral pharmacokinetic theory suggests an increased plasma level for a given dose of drug to be the cause of the age-related sensitivity to antipsychotics. Age-related changes in the metabolism and physiology of gastrointestinal, hepatic, renal, and cardiovascular systems are likely to contribute to this theory. However, there are several inconsistent findings concerning this theory. For example, age did not have an effect on the plasma level exposure of olanzapine in a study of patients with AD, and there was no relation between plasma levels and EPS in a different study with an elderly sample (Bigos et al., 2008; McCreadie 1992). In addition,

findings of a dissociation between the kinetics of plasma levels and D2/3 striatal occupancy suggests that the peripheral pharmacokinetic theory is unlikely to be the only factor responsible for the age-related heightened sensitivity to antipsychotic drugs (Tauscher et al., 2002). However, the possibility that peripheral pharmacokinetics may contribute to the overall increased sensitivity should not be excluded.

Central Pharmacokinetic Theory

The central pharmacokinetic hypothesis attributes the heightened sensitivity to increases in brain access and distribution for a given plasma level. Defects in the BBB could account for this, for example loosening of the tight junctions, or P-glycoprotein dysfunction (Brenner & Klotz 2004). P-glycoprotein regulates central concentrations of drugs by pumping back into the peripheral circulation. In support of this theory, higher BBB access of (R)-[¹¹C]verapamil (a substrate of P-glycoprotein) was found in elderly compared to younger subjects (Toornvliet et al., 2006). In addition, PET studies have demonstrated an age-related increase in radioactivity per given radiation dose, or plasma level, in the cerebellum; a region free of specific targets (Adams et al., 2004; Blin et al., 1993; Verhoeff et al., 2000). Age-related decline in endogenous dopamine levels have also been reported, including reduced levels of enzymes involved in the synthesis of dopamine (tyrosine hydroxylase and aromatic acid decarboxylase), and increased levels of enzymes involved in the catabolism of synaptic dopamine (MAO-B). A decline in endogenous dopamine removes competition for the receptor, resulting in increased binding for a given dose.

Pharmacodynamic Theory

The pharmacodynamic theory points towards an age-related decline in dopaminergic neurons (Cabello et al., 2002; Ma et al., 1999), and D2 receptors (Antonini et al., 1993; Kaasinen et al., 2000; Seeman et al., 1987), as the underlying cause of the heightened sensitivity seen in the elderly. This theory is of particular relevance to the increased sensitivity to antipsychotic drugs seen in AD, given the increased decline in D2 receptors compared to healthy ageing (Joyce et al., 1993; Joyce et al., 1998).

This theory proposes that for a given D2 occupancy level, an elderly patient will be more susceptible to clinical/adverse effects. An explanation for this theory is given by reference to the absolute number of D2 receptors required for normal motor function. The magnitude of biological response (i.e. motor control) is dependent on the absolute number of receptors occupied by endogenous dopamine, and so when the receptor population declines, the percentage of the total number of receptors required for normal motor function will be higher. As a result, a lower percentage of antipsychotic occupancy will cause interference with normal motor function (Uchida et al., 2009b).

5.1.2 Directly Assessing the Mechanisms of Heightened Sensitivity: Use of D2/3 Occupancy Studies

Although the literature suggests that the peripheral pharmacokinetic theory is unlikely to contribute independently to antipsychotic sensitivity in the elderly, the relevant contribution of the central pharmacokinetic and pharmacodynamic theories remains unclear. Only one study to date has directly assessed the relative contribution of each of these theories to antipsychotic sensitivity in the elderly (Uchida et al., 2009a). This study involved PET imaging and plasma sampling from 13 subjects with schizophrenia, aged 50 years and over, receiving risperidone at the time of the study. The results demonstrated that the relationship between striatal D2/3 occupancy and plasma drug levels was similar to that reported in younger patients, and hence did not support the central pharmacokinetic hypothesis of increased brain access or diminished endogenous dopamine (Nyberg et al., 1999; Remington et al., 1998; Uchida et al., 2009a). However, EPS were observed in seven subjects at D2/3 receptor occupancies much lower (34-79%) than the 80% threshold seen in young adults (Kapur 1998). The greater functional effect (EPS) for a given occupancy was taken to support the pharmacodynamic theory of antipsychotic sensitivity. Based on these findings, Uchida et al. (2009) postulated a lower 'therapeutic window' of D2/3 receptor occupancy in elderly schizophrenic patients, compared to the 60-80% reported in young adults (Kapur 1998). Preliminary data support this, whereby occupancies over 70% caused EPS and occupancies below 52% caused a relapse of symptoms in two subjects (Uchida et al., 2012). However,

interpretation of these findings is limited by the absence of baseline data on D2/3 receptor availability within the treated group; receptor occupancy was estimated using age-corrected measures from healthy older individuals. In addition, it is important that the range of psychotic disorders in the elderly receive individual consideration in terms of drug sensitivity.

To date, there has been no research specifically concerning the mechanisms of the increased sensitivity to antipsychotic drugs in people with AD, and no attempts to define a ‘therapeutic window’ of antipsychotic drug occupancy for this population. Likewise, there have been no attempts to determine the clinical relevance of extrastriatal D2/3 receptors to antipsychotic response in AD. This may in part be due to the fact that imaging techniques have not been sufficiently adapted for use in cognitively and neurologically impaired populations. For example, current scanning protocols require prolonged periods of time inside the scanner, which is not tolerable for many clinical populations. Chapter 4 tested the reliability of an adapted [¹⁸F]fallypride protocol, which used an interrupted scanning procedure and reduced the length of individual scanning sessions to 30 minutes. The protocol was highly reproducible in healthy older subjects, and remained so after reducing the length of individual scanning sessions to 20 minutes. The current study now aims to establish whether the adapted protocol is feasible for use in patients with AD, and to further optimise the protocol for use in D2/3 occupancy studies.

5.1.3 Aims

- (i) To assess the tolerability of the adapted (3 x 30 minute) protocol as a pre-treatment (baseline) protocol in people with AD who were about to commence antipsychotic medication for the management of behavioural or psychotic symptoms.
- (ii) To further adapt and optimise a post-treatment imaging protocol, which would take into account the reduction in available dopamine D2/3 receptor sites as a result of drug occupancy.
- (iii) To establish whether sampling times could be further reduced to 20 minute sessions in pre- and post-treatment protocols without affecting D2/3 occupancy values.

5.2 Methods

A brief overview of the methodology involved in the recruitment/screening procedure, PET imaging, and clinical assessment of subjects is given in Chapter 2, Sections 2.6 & 2.7. The scanning protocols used for pre- and post-treatment scans are detailed below.

5.2.1 Pre-Treatment Protocol

Image data were collected using the adapted [¹⁸F]fallypride imaging protocol described in Chapter 2, Section 2.5.3. This consisted of three scanning sessions: 0-30 minutes, 60-90 minutes, and 210-240 minutes. The initial 3 minutes of the first scanning session acquired frames with short duration (1 x 10 seconds, 10 x 5 seconds, 6 x 10 seconds, and 3 x 20 seconds). The remaining 87 minutes of scanning were acquired using frame lengths of 1 minute.

5.2.2 Post-Treatment Protocol

The scanning times used are adapted from [¹⁸F]fallypride protocols used in occupancy studies carried out in young adults (Kegeles et al., 2008; Kessler et al., 2006). The difference in timings between pre- and post-treatment protocols is to take into account the fact that occupancy of D2/3 receptors by antipsychotic medication lowers the number of available receptor sites, thus reducing the time taken to achieve equilibrium. The data was still collected during three scanning sessions, albeit at different time intervals: 0-20 minutes to provide an input function; 40-60 minutes to capture peak tracer binding in extrastriatal regions; and 110-150 minutes to capture peak binding within the striatum. The initial 3 minutes of the first scanning session acquired frames with short duration (1 x 10 seconds, 10 x 5 seconds, 6 x 10 seconds, and 3 x 20 seconds). The remaining 77 minutes of scanning were acquired using frame lengths of 1 minute.

5.2.3 Optimising the Protocol

In order to establish whether sampling times could be further reduced to 20 minute sessions in pre- and post-treatment protocols without affecting D2/3 occupancy

values, two sets of analyses were performed. Data were first analysed using the complete data set from three scanning sessions of 30 minutes, and then were reanalysed using only 20 minutes of data from each scanning session. The two analyses are referred to as follows: Method 1, pre-treatment (0-30, 60-90 and 210-240 minutes), post-treatment (0-20, 40-60 and 110-150 minutes); and Method 2, pre-treatment (0-20, 70-90 and 220-240 minutes), post-treatment (0-20, 40-60 and 130-150 minutes).

5.2.4 Defining ROIs

The cerebellar reference region was defined using the Automated Anatomical Labelling atlas (Tzourio-Mazoyer et al., 2002), and the Tziortzi atlas was used to define the caudate, putamen, and extrastriatal regions; thalamus and inferior temporal cortex (Tziortzi et al., 2011). These regions were chosen to allow comparison with previous occupancy studies (Xiberas et al., 2001b), and studies investigating optimum scan durations (Vernaleken et al., 2011). The striatal subdivisions were defined using a template which was originally defined using the same anatomical landmarks as Mawlawi et al. (2001), described in Chapter 2, Section 2.7.4.

5.2.5 Movement Correction

Head movement was monitored by a video camera, which took still pictures of the patient's head position at 1-second intervals. The images were converted into video format (avi) using PhotoLapse 3 software, and time compressed (15 frames per second). Time of head movement was recorded from the video and cross-referenced with the subject's time-activity curves and dynamic PET images. Upon visual inspection, if movement from the video correlated with anomalies on the time-activity curves or blurred dynamic images, the relevant 1-minute frames were deleted. This technique of movement correction was needed in addition to the frame-to-frame realignment discussed in Chapter 2, in order to account for sudden movements within each frame.

5.2.6 Statistics

The regional percentage change in [¹⁸F]fallypride BP_{ND} derived using Method 2 as opposed to Method 1 was calculated as follows: $(|Method\ 1 - Method\ 2|/Method\ 1)*100$, and is expressed as the mean and SD across subjects, for both pre- and post-treatment scans. Regional D2/3 receptor occupancy was determined by the following calculation: $(|PreTreatment\ BP_{ND} - PostTreatment\ BP_{ND}|/PreTreatment\ BP_{ND})*100$, and was performed on data derived from Methods 1 and 2. The absolute difference between the calculated percentage occupancies from Methods 1 and 2 was determined by $|Occupancy\ Method\ 1 - Occupancy\ Method\ 2|$ and expressed as the mean and SD across subjects.

5.3 Results

5.3.1 Clinical and Demographic

Pre-Treatment Scan

Eight subjects were recruited to the study, but two were unable to follow through with a baseline scan; one because of delusional preoccupation and a belief that research staff were colluding in this, and a second was withdrawn from the study because of deteriorating cardiorespiratory disease, which meant that he was not able to tolerate the scan or eligible to receive amisulpride.

Of the remaining six subjects, all were able to tolerate the baseline scan, apart from one subject who failed to complete the final 30 minute scanning session (210-240 minutes post-injection). This is likely due to a 90 minute delay in tracer delivery to the PET unit, which considerably extended the length of time that the subject spent in the department. For this subject, image data collected during the first two scanning sessions were used to determine BP_{ND}, and a bias correction (calculated from the five completed pre-treatment scans) was applied. The bias correction was determined by comparing BP_{ND} calculated using only the first two scanning sessions (2 x 30 minutes) to the full dataset (3 x 30 minutes) (shown in Table 5.1). The bias corrected BP_{ND} values are used for the remainder of the calculations in this chapter.

Table 5.1: Bias Corrected Pre-Treatment BP_{ND}

Region	Method 1		Method 2	
	Original	Bias Corrected	Original	Bias Corrected
	BP _{ND} ¹	BP _{ND} (min-max) ²	BP _{ND} ¹	BP _{ND} (min-max) ²
Caudate	10.60	12.37 (11.53-12.72)	9.74	11.98 (11.54-12.39)
Putamen	14.78	17.75 (16.99-18.45)	13.86	17.46 (16.56-18.02)
Limbic striatum	11.80	13.90 (12.76-14.85)	11.19	13.67 (12.30-14.40)
Associative striatum	11.50	13.96 (13.49-14.67)	10.74	13.63 (12.90-14.25)
Sensorimotor striatum	13.04	15.86 (15.10-16.72)	12.21	15.57 (14.80-16.24)
Thalamus	1.35	1.31 (1.11-1.47)	1.32	1.30 (1.09-1.44)
Inferior temporal gyrus	0.44	0.35 (0.30-0.39)	0.44	0.34 (0.26-0.39)

¹Original BP_{ND} with last scan missing (2x30mins); ²BP_{ND} corrected by average (minimum and maximum) % bias: % bias calculated as $[(BP_{ND} (2x30) - BP_{ND} (3x30))/BP_{ND} (3x30)]*100$ (Method 1) and $[(BP_{ND} (2x20) - BP_{ND} (3x20))/BP_{ND} (3x20)]*100$ (Method 2) using data from five completed pre-treatment scans in the current study.

Post-Treatment Scan

Of the original six subjects, four returned for the post-treatment scan; one was unable to tolerate amisulpride because of an increased frequency of falls, and one was withdrawn because of unrelated physical health problems. The remaining four subjects responded well to 50mg amisulpride daily. The mean reduction in the three-item NPI score was $62.6 \pm 22.9\%$, with a range between 36.4-100%. EPS were present in a single subject and were minimal (score of 0.2 on the SAS). Sedation was reported as a side effect in three subjects, two at a mild level (increased evening sleepiness) and one at a slightly more moderate level (sedation extended to the next day). The subject with moderate sedation received a reduction in the dose of amisulpride (50mg to 25mg) prior to the post-treatment scan. Of the four subjects, three were scanned after 28 ± 7 days treatment with amisulpride 50mg, and the fourth was scanned after 47 days treatment (26 days at 50mg, followed by 21 days at 25mg). The clinical and demographic data of the six subjects who had a baseline scan can be seen in Table 5.2.

Table 5.2: Clinical and Demographic data

Age (years)	81	91	89	85	76	88
Gender	Male	Female	Male	Female	Male	Female
MMSE	15	14	13	18	19	17
Sensory deficits	Hearing and Vision	Hearing and Vision	Hearing and Vision	-----	Vision	-----
Impaired mobility	Yes	Yes	Yes	No	No	No
Living arrangements	Own home, with carer	Own home, with carer	Own home, formal live-in carer	Care Home	Lives alone	Own home, with carer
<i>Baseline symptoms</i>						
Delusions	12	6	12	8	8	8
Hallucinations	9	8	12	0	12	8
Agitation	8	0	9	6	0	8
Total score	27	14	33	14	20	24
Prescribed cognitive enhancer(s)	No	Yes	Yes	Yes	Yes	Yes
Prescribed benzodiazepine(s)	No	No	Yes	No	No	No
Amisulpride dosage at time of second scan	–	–	50mg	25mg γ	50mg	50mg
Duration of treatment	5 days – discontinued due to unrelated physical health problems	Failed to tolerate 25mg stopped after 14 days due to increased falls	28 days	26 days at 50mg; 21 days at 25mg	35 days	21 days
% reduction in total symptom score	–	–	36.4	100	60	54.2
SAS Score	–	–	0	0	0	0.2

γ 100% response to 50mg nocte, but required dose reduction to 25mg nocte because of excessive sedation. The response was sustained at 25mg.

Head Movement

Head movement correction was required in all subjects, pre- and post-treatment, and is shown graphically in Figure 5.2. The Figure shows the time-activity curve for the caudate only, in subjects with pre- and post-treatment data.

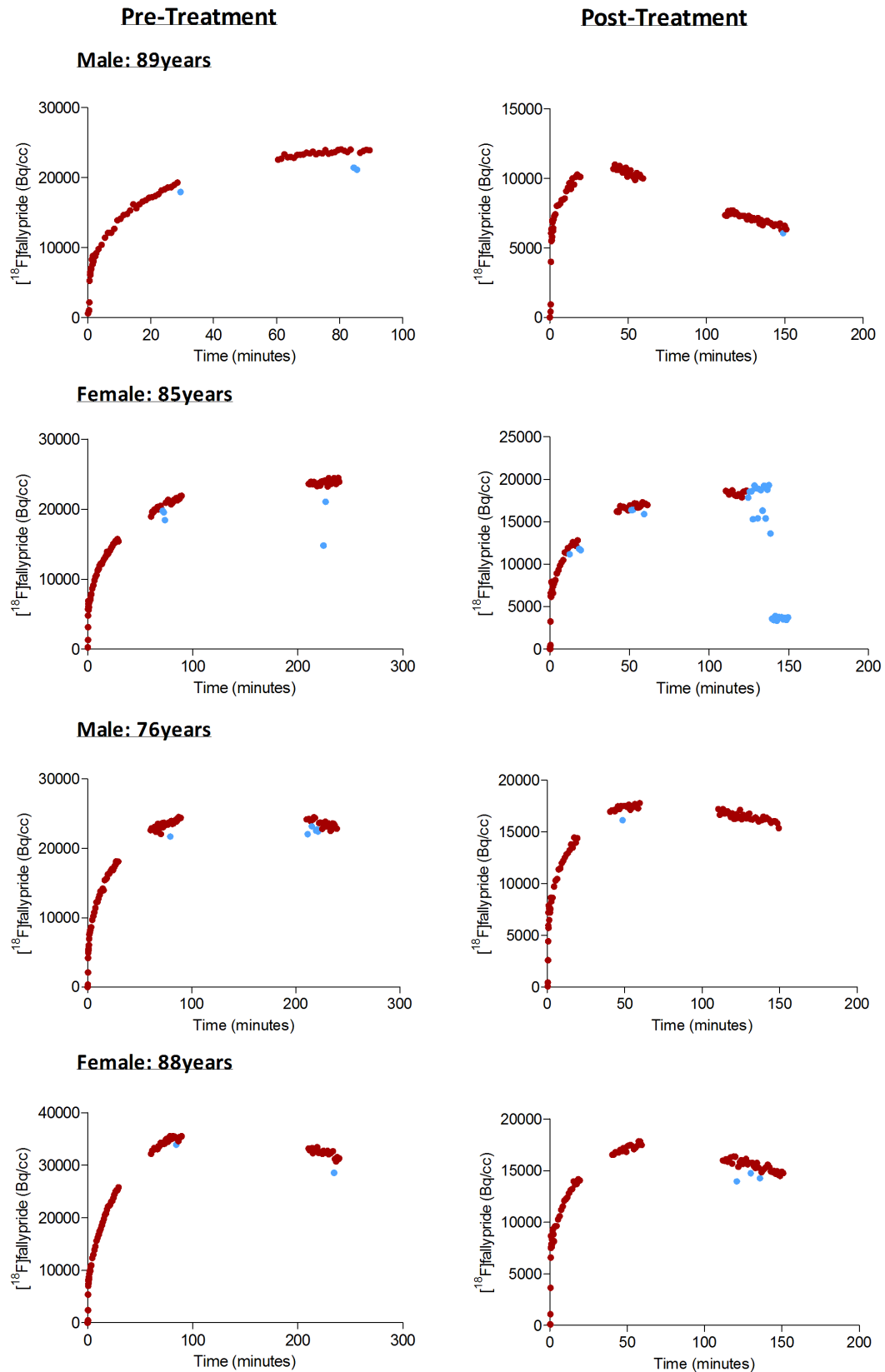
Pre-Treatment

During the baseline scan, minimal frames were removed: 0-30 minutes, one 60-second frame was removed in one subject; 60-90 minutes, a maximum of three 60-second frames were removed; 210-240 minutes, a maximum of five 60-second frames were removed.

Post-Treatment

Head movement in the first two scanning sessions of the post-treatment scan was minimal, requiring the removal of a maximum of three 60-second frames across the four subjects. However, movement in the third scanning session was greater, requiring the removal of 26 60-second frames in one subject (85 years, female). The post-treatment scan for this subject was excluded from the analysis due to excessive movement. This is the same lady who reported moderate sedation and was given a reduced dose of amisulpride (25mg) prior to the post-treatment scan.

Figure 5.2: Time-Activity Curves for the Caudate, Showing 60-Second Frames Removed (blue) From Each Scanning Session (Method 1)



5.3.2 Regional D2/3 Receptor Binding

Comparison of Methods

Pre-Treatment

Mean (SD) regional pre-treatment BP_{ND} (Method 1 and Method 2) is described and compared in Table 5.3. The mean percentage change in BP_{ND} between the two methods was <2.5% in all regions but the inferior temporal cortex, where the average percentage change was 3.51%.

Post-Treatment

Regional post-treatment BP_{ND} (Method 1 and Method 2) for the three subjects is presented in Table 5.4. Mean percentage variability in BP_{ND} across the two methods was <2% in all regions but the inferior temporal cortex, where the variability was 4.31%.

Table 5.3: Pre-Treatment Scan: Percentage Change in [¹⁸F]fallypride BP_{ND} Between Method 1 (3 x 30 minutes) and Method 2 (3 x 20 minutes)

Region	Method 1 ¹	Method 2 ¹	Mean (SD) % change ²
Caudate	15.66 (2.37)	15.62 (2.53)	2.20 (0.91)
Putamen	21.31 (2.47)	21.31 (2.48)	1.95 (0.52)
Limbic striatum	16.51 (1.98)	16.44 (2.06)	1.77 (0.87)
Associative striatum	17.22 (2.37)	17.20 (2.42)	1.99 (0.53)
Sensorimotor striatum	19.64 (2.69)	19.66 (2.80)	1.89 (0.50)
Thalamus	1.39 (0.24)	1.39 (0.25)	1.41 (0.86)
Inferior temporal gyrus	0.43 (0.26)	0.43 (0.26)	3.51 (2.72)

¹Pre-Treatment BP_{ND} given as mean across subjects (SD), mean includes bias corrected BP_{ND} for one subject; ²(|Method 1-Method 2|/Method 1)*100

Table 5.4: Post-Treatment Scan: Percentage Change in [¹⁸F]fallypride BP_{ND} Between Method 1 (20, 20, 40 minutes) and Method 2 (3 x 20 minutes)

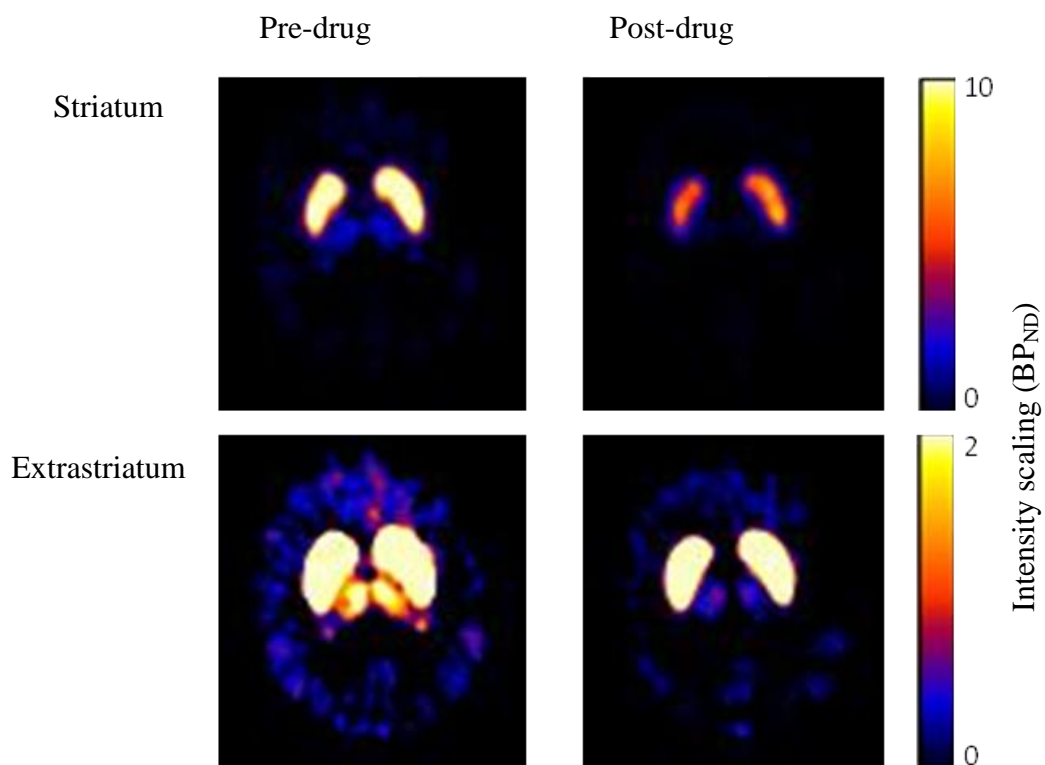
Subject:(Age/gender)	1: 89/Male		2: 76/Male		3: 88/Female		Mean (SD) % change (n = 3) ¹
	[¹⁸ F]fallypride BP _{ND}						
Region	Method 1	Method 2	Method 1	Method 2	Method 1	Method 2	
Caudate	3.71	3.77	9.22	9.29	4.97	5.02	1.13 (0.44)
Putamen	7.65	7.81	15.09	15.19	9.03	9.16	1.37 (0.67)
Limbic striatum	6.04	6.15	11.31	11.32	7.68	7.80	1.17 (0.93)
Associative striatum	5.11	5.18	10.72	10.76	6.28	6.36	1.01 (0.56)
Sensorimotor striatum	6.86	7.02	15.13	15.26	8.38	8.44	1.37 (0.82)
Thalamus	0.32	0.32	0.82	0.82	0.37	0.37	0.93 (0.54)
Inferior temporal gyrus	0.23	0.24	0.53	0.54	0.23	0.24	4.31 (1.55)

¹(|Method 1-Method 2|/Method 1)*100

5.3.3 Regional D2/3 Receptor Occupancy

Figure 5.3 shows a parametric PET image of [^{18}F]fallypride binding, before and after amisulpride treatment in one subject (88 years, female). The reduced colour intensity, from approximately 10 to 5 in the striatum and 1.5 to 0.5 in the extrastriatal regions, clearly illustrates a reduction in [^{18}F]fallypride binding after 21 days of 50mg amisulpride.

Figure 5.3: Parametric Image of [^{18}F]fallypride Binding Pre and Post Amisulpride



Regional D2/3 occupancy was calculated using pre- and post-treatment BP_{ND} for both Methods 1 and 2. Time-activity curves showing pre- and post-treatment data for Method 1 are shown in Figures 5.4, 5.5 and 5.6; representing the caudate and putamen, functional striatal subdivisions, and extrastratial regions, respectively. The Figures illustrate the regional D2/3 occupancy in each of the three subjects with pre- and post-treatment data. Using the original protocol (Method 1), a higher striatal occupancy was seen in the caudate (46.66-72.39%), compared to the putamen (30.03-60.05%). The functional subdivisions of the striatum also showed a gradient of occupancy, the highest being the associative striatum (40.01-66.65%), followed

by the limbic striatum (34.55-60.05%) and sensorimotor striatum (31.83-60.14%). Amongst the extrastriatal regions, the thalamus showed a higher occupancy (53.80-76.07%) than the inferior temporal gyrus (26.88-42.54%). The same pattern of occupancy was seen across both methods. The absolute difference in percentage occupancies between the two methods was <2% in all regions, apart from the inferior temporal gyrus, which showed an average difference of 6.11% between methods. A comparison of the two methods is shown in Table 5.5. Across the three subjects, subject one (89 years, male) showed the highest D2/3 receptor occupancy across all regions. The lowest occupancies were seen in subject two (76 years, male) across all regions, apart from the inferior temporal gyrus, which was lowest (26.88%) in subject three (88 years, female).

Figure 5.4: Time-Activity Curves Showing Striatal D2/3 Receptor Occupancy

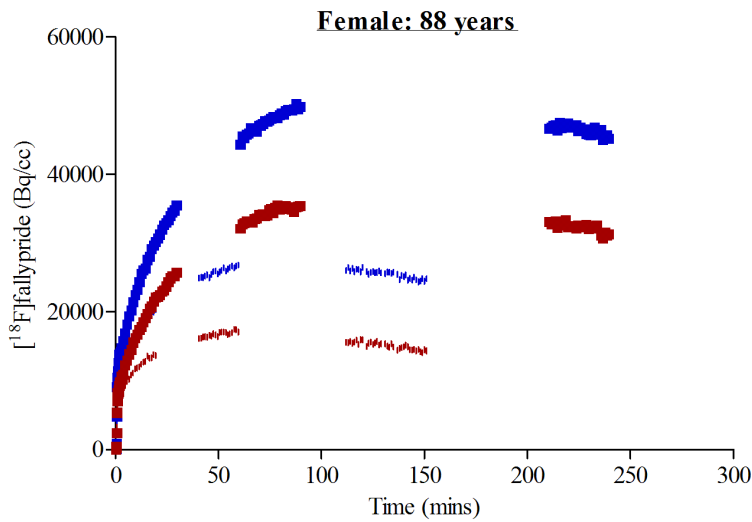
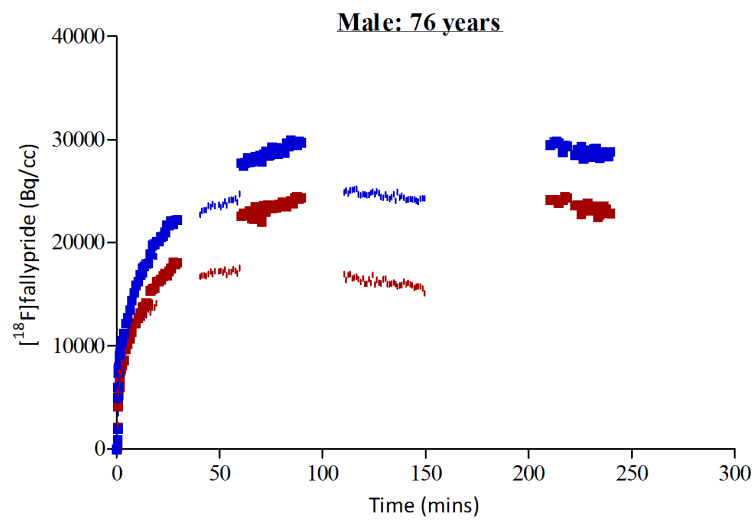
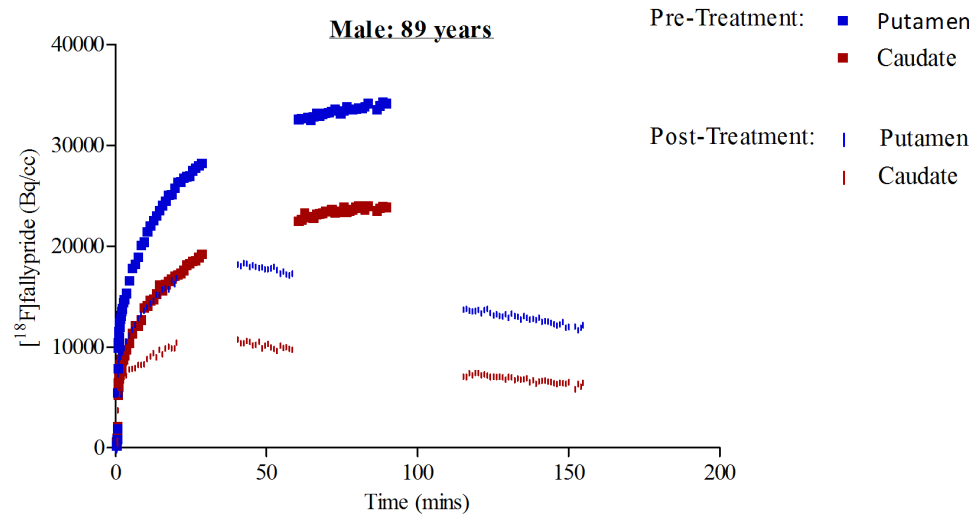


Figure 5.5: Time-Activity Curves Showing Striatal Subdivisions D2/3 Receptor Occupancy

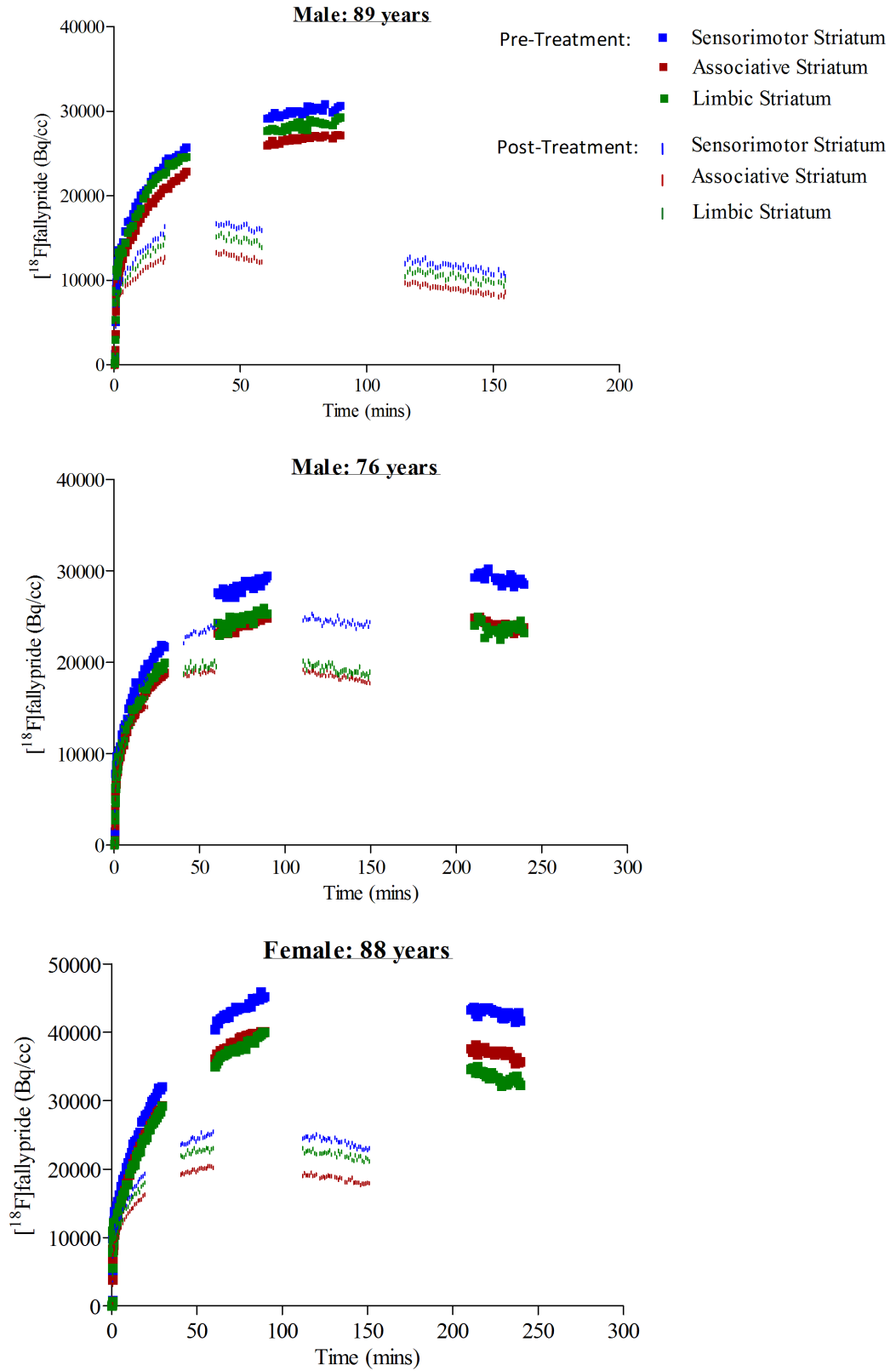


Figure 5.6: Time-Activity Curves Showing Extrastriatal D2/3 Receptor Occupancy

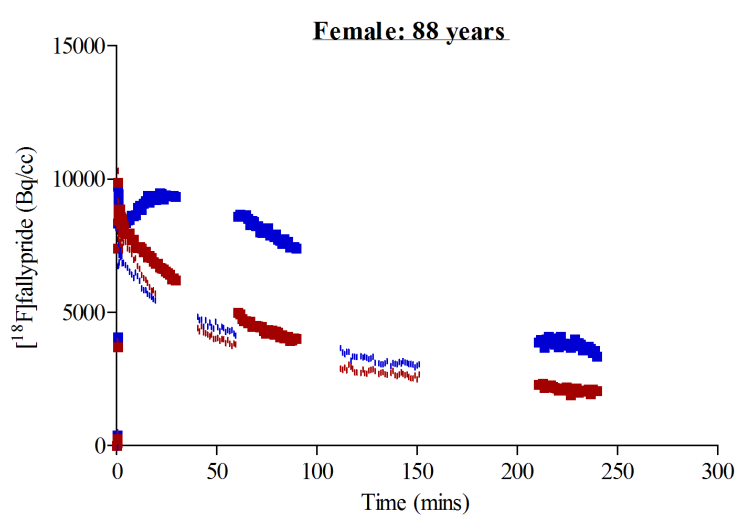
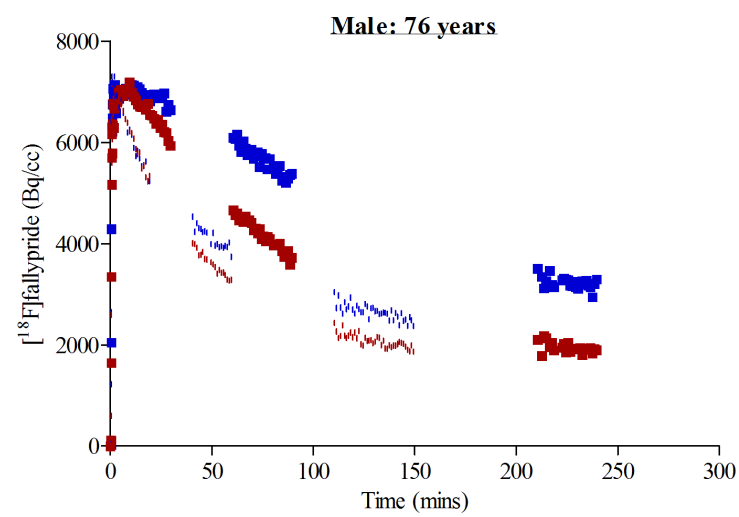
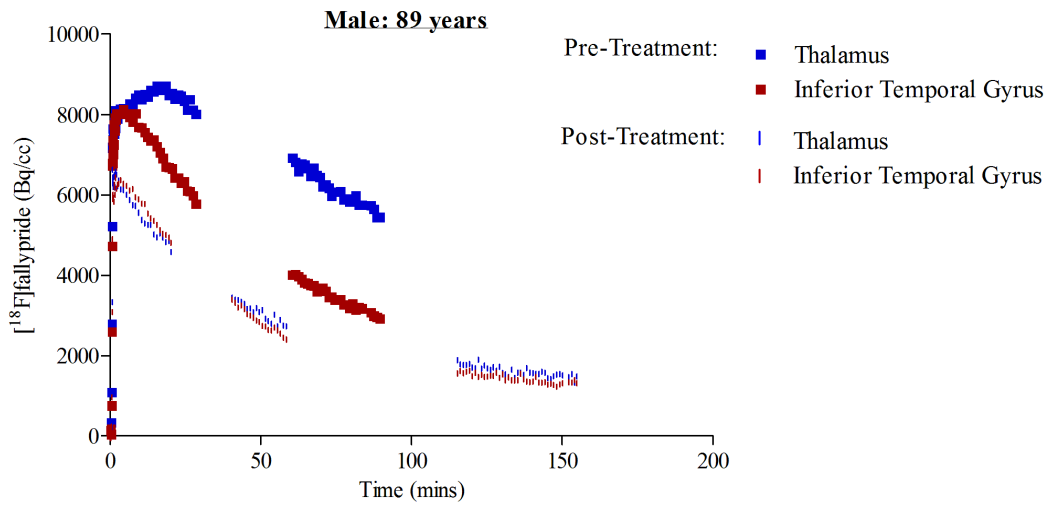


Table 5.5: Regional Dopamine D2/3 Receptor Occupancy During Treatment With Amisulpride 50mg Daily: Comparison of Method 1 and Method 2

Subject (Age/Gender)	89/Male*		76/Male		88/Female		Mean (SD) % difference ³
Region	Percentage occupancy of D2/3 receptors						
	Method 1 ¹	Method 2 ²	Method 1 ¹	Method 2 ²	Method 1 ¹	Method 2 ²	
Caudate	69.97	68.50	46.66	47.00	66.09	62.25	1.88 (1.46)
Putamen	56.89	55.27	30.03	30.87	58.34	57.15	1.22 (0.32)
Limbic striatum	56.55	55.00	34.55	33.86	49.53	47.87	1.30 (0.43)
Associative striatum	63.39	62.00	39.28	40.01	62.97	61.95	1.05 (0.27)
Sensorimotor striatum	56.75	54.96	30.90	31.83	58.06	57.13	1.22 (0.41)
Thalamus	75.82	75.36	53.80	54.08	70.62	70.53	0.28 (0.15)
Inferior temporal gyrus	36.45	31.11	42.54	40.58	26.88	15.84	6.11 (3.75)

¹: Percentage Occupancy Method 1: ((PreTreatment 3x30minutes – PostTreatment 20, 20, 40minutes)/PreTreatment 3x30minutes)*100

²: Percentage Occupancy Method 2: ((PreTreatment 3x20minutes – PostTreatment 3x20minutes)/PreTreatment 3x20minutes)*100

³: Absolute difference between occupancies derived from Method 1 vs. Method 2: |Occupancy Method 1 – Occupancy Method 2|

* Final 30 minutes of pre-treatment scan missing. The raw BP_{ND} values have been corrected using estimated % bias data (see Table 5.1)

5.4 Discussion

The first objective of the current study was to determine whether the recently adapted [¹⁸F]fallypride protocol (Chapter 4) was suitable for use in a clinically relevant population, and to assess the quality of the resulting image data.

Generally, the protocol translated well for use with AD subjects, with only one of the six subjects failing to complete all three scanning sessions. For this scan, the tracer was delivered to the unit 90 minutes behind schedule, meaning the subject had an extended stay in the department. The waiting time appeared more problematic than the scan itself, which could have been due to several factors, such as: osteoarthritic pain, which caused discomfort when seated in the wheelchair for long periods of time; fatigue, due to several nights of disturbed sleep; and disorientation, caused by a combination of sensory and cognitive impairment. This patient was able to tolerate the first two scanning sessions with very little head movement, and so the image data was bias corrected and included in the analysis.

A number of the patients in the present sample needed reassurance whilst in the scanner, and this created more head movement compared to that seen in the previous study with healthy adults (Chapter 4). However, movement was minimal in most cases, and image quality was preserved by performing frame-to-frame realignment and removing 60-second frames where motion had occurred. Nevertheless, the possibility that subtle head movements may have impacted on the quality of data should not be excluded.

The second objective was to adapt and optimise a post-treatment [¹⁸F]fallypride imaging protocol to enable peak tracer binding in extrastriatal and striatal regions to be captured. The first two (20 minute) scanning sessions were generally well tolerated, with minimal head movement. However, the final (40 minute) session proved more difficult and produced poor quality data in one subject. The subject was unable to tolerate more than 15 minutes of the final scan, resulting in the post-treatment scan being excluded from the analysis.

The third aim of the study was to establish whether reducing the sampling times further, to 20 minute scanning sessions, would have an impact on the occupancy data collected. Reducing the duration of individual scanning sessions had minimal effect on pre- and post-treatment BP_{ND} in the striatal regions and thalamus (<2.5%), and

the inferior temporal gyrus (<5%). The impact of the reduced scan durations on the calculated occupancy values was also minimal (<2%) in all but the inferior temporal gyrus, where the discrepancy between methods ranged from 1.96% to 11.04%. The variability observed here could be due to a low signal to noise ratio of [¹⁸F]fallypride binding in the temporal cortex, and the additional impact of AD on D2/3 receptor density in this region (Joyce et al., 1998).

5.4.1 Dose-Occupancy Relationships

Amisulpride is a highly selective antagonist for D2/3 receptors, and in young adults achieves occupancies of 65% or above in striatal and extrastriatal regions, within the optimal clinical dose range (400-800mg daily) (Sparshatt et al., 2009). Occupancy data on very low dose amisulpride (50mg) is limited and varies considerably between studies. The first PET study to examine striatal D2/3 binding in response to amisulpride achieved occupancies ranging from 3-9%, using [⁷⁶Br]bromolisuride (Martinot et al., 1996). The same group reported 0% striatal D2/3 receptor occupancy when using the high affinity radioligand [⁷⁶Br]FLB-457 (Xiberas et al., 2001a). In contrast to the low striatal occupancies reported in the above PET studies, research using SPECT techniques, and the [¹²³I]IBZM radiotracer, reported occupancies of 40% in the striatum (la Fougère et al., 2005; Meisenzahl et al., 2008). These studies suggest that the discrepancies observed in occupancy data are due to differences in methodology, including the choice of radiotracer and imaging technique used. The timing of drug dose relative to the scan and treatment duration are also important methodological issues to consider when comparing occupancy data, particularly when plasma concentrations are not available (Meisenzahl et al., 2008).

Data on amisulpride D2/3 occupancy in extrastriatal regions consists of only one study using PET imaging, which reported occupancy values of 30-40% in the thalamus, and a range of 48-65% occupancy in the temporal cortex (Xiberas et al., 2001b).

In the present study, we observed the expected gradient of occupancy (caudate > putamen) in all three subjects (Stone et al., 2005; Vernaleken et al., 2004). In terms of specific occupancy values, striatal occupancy in one subject (76 year old male)

was within a similar range to that reported in the above literature in young adults. However, the occupancy values in the other two subjects (89 year old male, 88 year old female) are considerably higher. With regards to the extrastriatal regions, occupancy values in the thalamus exceeded those in young adults, whereas occupancies in the inferior temporal cortex were lower than expected, particularly so in one subject (26.88%).

5.4.2 Methodological Issues

Several methodological issues may have impacted on the accuracy of the current results. For example, additional noise was introduced to the data by the bias correction applied to the pre-treatment scan. Nevertheless, this method prevented the loss of data, and the fact that the bias was calculated based on pre-treatment scans from the same sample will have minimised the noise. It was not possible to apply a bias correction to the post-treatment scan as there was insufficient data to calculate an average bias. As a result, one post-treatment scan was excluded from analysis due to excessive head movement. Due to the small sample size, lack of information on plasma levels of amisulpride, and additional noise created by including bias corrected data, it is difficult to determine whether the higher striatal and thalamic occupancies seen in the two older subjects are due to changes in peripheral pharmacokinetics (i.e. an age-related increase in the plasma level of amisulpride), changes in central pharmacokinetics, or pharmacodynamic changes. It could, of course, be a combination of all three, and this will need to be explored in future studies with an adequate sample size to examine such relationships. However, the primary aim of this study was not to determine dose-occupancy relationships, but to establish the tolerability of the adapted [^{18}F]fallypride protocol, and optimise it for use in future studies.

Other methodological issues which should be considered include the lack of MRI, and partial volume effects. These factors are discussed in Chapter 6, Section 6.2.3. Partial volume effects are likely to have impacted most in regions where atrophy is more marked in AD, particularly the inferior temporal gyrus. Atrophy, together with low specific binding in this region, may have produced artefactually low occupancy values in the current study. The ability of the adapted [^{18}F]fallypride protocol to

image D2/3 receptors in the inferior temporal gyrus will need to be explored further, perhaps in different patient groups where atrophy in this region is less marked, for example in those with very late-onset schizophrenia-like psychosis.

5.4.3 Accuracy of Post-Treatment Protocol

A further consideration is the duration of the post-treatment scan, and the accuracy of the chosen sampling times in capturing peak [¹⁸F]fallypride binding in striatal and extrastriatal regions. This is an important consideration, as imaging before or after binding has reached a plateau in a particular region will result in inaccurate estimations of the BP_{ND}. This is particularly relevant to the striatal regions, where D2/3 receptor density is highest. Inaccuracies in BP_{ND} estimations, primarily caused by insufficient scan durations, can potentially influence the conclusions drawn from occupancy studies e.g. preferential extrastriatal binding of certain antipsychotic medication (Olsson & Farde 2001).

The current post-treatment protocol was determined from previous studies which have measured D2/3 receptor occupancy following antipsychotic treatment. These studies have collected data over a period between 180-240 minutes (Kessler et al., 2006), and during a single scanning session lasting 120 minutes (Kegeles et al., 2008). A more recent study specifically investigated the effect of scan duration on occupancy values, using [¹⁸F]fallypride data on young adults (N = 50) who were treated with a range of antipsychotic drugs; clozapine, ziprasidone, quetiapine and olanzapine. The results of the study indicated that equilibrium is achieved within 70 minutes post-injection in the extrastriatal regions (between 3.8 and 39.7 minutes in the thalamus; and 6.7 - 67 minutes in the inferior temporal cortex), and between 29.5 and 167 minutes in the putamen (Vernaleken et al., 2011).

Based on the findings of Vernaleken et al. (2011), it could be argued that the sampling times of the current study were too early to ensure peak tracer binding was captured. There is a possibility that this may have contributed to the lower occupancy values seen in the temporal cortex in all three subjects. However, it is unlikely to have had an effect on striatal values, as the antipsychotic drugs used in the above study have considerably lower striatal occupancies than is typically observed during amisulpride treatment (Kessler et al., 2005; Kessler et al., 2006;

Vernaleken et al., 2004), and would therefore result in a longer time for the tracer to achieve equilibrium in this region.

5.5 Conclusion

Overall, the current study has demonstrated the suitability of the adapted [¹⁸F]fallypride protocol for use in D2/3 receptor occupancy studies in older adults with AD. The study also highlights the importance of avoiding unnecessary delays and re-orienting subjects to their surroundings during scanning sessions, in order to maximise tolerability to the imaging procedure. However, after taking these factors into account, the protocol demonstrates tolerability in subjects who are both cognitively and behaviourally disturbed, and hence enables the advancement of research in this population. The next stage of the research will use the adapted protocol in a larger sample, including subjects with late-onset schizophrenia and those with AD, to determine the relationship between drug dose, plasma levels and regional occupancy. This research will aim to define the ‘therapeutic window’ of D2/3 occupancy in older adults, and will further explore the mechanisms involved in the heightened sensitivity to antipsychotic drugs observed in the elderly. Future work will also aim to refine the image analysis technique in relation to the inferior temporal cortex, to allow the contribution of extrastriatal occupancy to be further explored.

Chapter 6: Final Discussion

This chapter summarises the main findings of the thesis, and the limitations involved in interpreting the results. The implications of the main findings will then be discussed, together with suggestions for future research.

6.1 Summary of Main Findings

6.1.1 Establishing the Neuropsychological Profile of Psychotic Symptoms in AD

The first component of the thesis aimed to investigate the neuropsychological profile of psychotic symptoms in AD, and to establish if neuropsychological tests known to be associated with striatal D2/3 receptor function might act as ‘cognitive markers’ of psychotic symptoms in AD.

The primary analysis addressed the hypothesis that tests which correlate with dopamine function would differ between psychotic and non-psychotic AD patients. This hypothesis was based on the finding that increased D2/3 receptor availability was associated with delusions in AD, as well as with poorer sustained attention (indexed by reduced accuracy of RVP performance) and increased motor speed (indexed by reduced latency on a motor screening test) in the same sample (Reeves et al., 2009; Reeves et al., 2010). Consistent with this hypothesis, RVP accuracy was reduced in the current psychotic group, after controlling for global cognition, years of education and age. Poorer sustained attention in the psychotic group could represent differential influences of the dopamine D1 receptors in the prefrontal cortex versus D2 receptors in the striatum; explained by fronto-striatal-thalamic circuitry (Chapter 1, Section 1.2.1) and the inverted U-shaped curve of dopaminergic function and cognitive performance (Arnsten 1997; Goldman-Rakic et al., 2000).

In contrast, there was no significant between-group difference on the SRT task, which was chosen as a more robust measure of motor speed than the motor screening test (MOT). This finding could be due to the insensitivity of the SRT task to measure dopaminergic function (Pullman et al., 1990; Starkstein et al., 1989). However, the fact that motor latency did not differ between the two groups when measured by the MOT task either, suggests that motor speed may not be a sensitive marker of psychotic symptoms in AD. The lack of sensitivity of the motor tasks could be due

to age-related sensory deficits or osteoarthritis impacting on performance. Alternatively, the results could indicate that motor function and psychotic symptoms are predominantly controlled by different functional subdivisions of the striatum. Motor function is associated with dopaminergic function in the sensorimotor striatum (Graybiel et al., 1994; Reeves et al., 2010), whereas presynaptic dopaminergic function in the associative striatum has been implicated in delusions within the context of schizophrenia (Howes et al., 2007; Kegeles et al., 2010). Therefore, tasks linked to the associative striatum may be more sensitive cognitive markers of psychotic symptoms in AD.

The present study also aimed to establish the neuropsychological profile of psychotic symptoms in AD, and included a neuropsychological test battery covering five cognitive domains: executive function, memory, language, constructional praxis and visuoperceptual function. After controlling for global cognition, years of education and age, significant between-groups differences were only observed on one task (Incomplete Letters), which was part of the visuoperceptual function domain. This finding remained significant after applying Bonferroni corrections for multiple comparisons. A trend-level significance ($p = 0.053$) was also observed for between-group differences in Object Decision, a second task within the visuoperceptual function domain. Both the Incomplete Letters task and Object Decision task are measures of object perception, a process thought to be controlled by the ventral visual pathway (Mishkin et al., 1983). Therefore, the impaired performance in the psychotic group may be explained by a disruption to the above pathway.

A secondary aim of the present thesis was to further explore significant between-group differences in neuropsychological test performance in terms of paranoid (persecutory delusions) and misidentification (misidentification delusions and/or visual hallucinations) subtypes. The results demonstrate that the significant between-group differences observed in the RVP and Incomplete Letters tasks were driven predominantly by the misidentification subgroup, who presented solely with misidentification delusions and hallucinations. The misidentification group performed significantly poorer than the non-psychotic group on the RVP task, and significantly worse than all the groups on the Incomplete Letters task. The fact that there was no significant difference between the individual delusional subtypes on the RVP task could indicate that D2/3 receptor availability is increased along a

continuum, from subtle increases in the paranoid group, to more marked increases in the misidentification subgroup. The greater the increase in D2/3 receptor availability, the more impaired the performance on the RVP task. Hence the difference in performance between the misidentification subgroup and non-psychotic group reached statistical significance. However, the fact that the misidentification subgroup performed significantly worse than the paranoid group on the Incomplete Letters task could indicate that additional pathology is contributing to the observed perceptual deficits, which is distinct to the misidentification subgroup. A proposed neural framework for object-processing suggests that the ventral visual pathway is part of a highly interactive occipito-temporal network, which projects to multiple areas including limbic and frontal regions (Kravitz et al., 2013). The fact that more marked pathology is reported in the limbic structures (specifically the hippocampus and its projection zones - parahippocampal gyrus and transentorhinal cortex) of subjects with misidentification phenomena, but not persecutory delusions (Forstl et al., 1994; Mukaetova-Ladinska et al., 1993; Sweet et al., 2000) (reviewed by Reeves and colleagues 2012), and that hypometabolism has been observed in the frontal regions of AD subjects with misidentifications (Mentis et al., 1995), supports the suggestion of distinct ventral visual pathway disturbances in this group.

A further secondary aim of the current study was to examine whether neuropsychological test performance can predict the odds of psychotic symptoms in AD patients. The RVP and Incomplete Letters tasks were thus entered into a logistic regression analysis to determine their ability to act as predictors of psychotic symptoms in AD. Whilst the Incomplete Letters task demonstrated a significant independent contribution to the presence of psychotic symptoms, the RVP did not (as shown by a non-significant effect of RVP when entered into the regression model with the Incomplete Letters task). This result suggests that group differences in the two tasks may be primarily underpinned by a visuo-perceptual component.

6.1.2 Establishing the Test-Retest Reliability of an Adapted [¹⁸F]fallypride Imaging Protocol for Use in Older People

The second component of the present thesis aimed to adapt [¹⁸F]fallypride imaging for use in healthy older people, by using an interrupted scanning protocol which

considerably shortened the length of time spent in the scanner, so that individual sessions lasted only 30 minutes.

The adapted protocol demonstrated high reproducibility and reliability across the striatum, consistent with previous test-retest studies using [¹⁸F]fallypride in young adults (Cropley et al., 2008; Mukherjee et al., 2002). Within extrastriatal regions, high reproducibility (<8% variance) was seen in all but the prefrontal regions (orbitofrontal and anterior cingulate cortices), in particular the anterior cingulate cortex, where BP_{ND} differed by 28.84% between test and retest scans.

A secondary aim of Chapter 4 was to identify whether sampling times could be further reduced to 20 minute sessions without affecting the reliability of the method. The shorter scanning sessions produced the same pattern of reproducibility as the original 30 minute protocol, across striatal and extrastriatal regions. Test-retest variability increased minimally (<3.2%) in all regions except the anterior cingulate cortex, where the increase was more substantial (14.47%).

6.1.3 Optimising [¹⁸F]fallypride Imaging for D2/3 Occupancy Studies in AD

The third component of the present thesis aimed to optimise the adapted [¹⁸F]fallypride imaging protocol for use in D2/3 occupancy studies in patients with AD. There were three specific aims to this study (Chapter 5).

The first aim was to assess the tolerability of the adapted (3 x 30 minute) protocol as a pre-treatment (baseline) protocol in people with AD who were about to commence amisulpride for the management of behavioural and psychotic symptoms. The protocol translated well for use with AD subjects, with only one subject failing to complete all three scanning sessions, because of a long delay in tracer delivery as opposed to the scan itself.

The second aim was to further adapt and optimise a post-treatment imaging protocol, taking into account the reduction in available dopamine D2/3 receptor sites as a result of drug occupancy. The post-treatment protocol involved three scanning sessions, two lasting 20 minutes and the final scan lasting 40 minutes. Whilst the first two scanning sessions were well tolerated, the final scan proved more difficult, and produced poor quality data in one subject due to excessive head movement.

The final aim of the study was to establish whether sampling times could be further reduced to 20 minute sessions in pre- and post-treatment protocols without affecting D2/3 occupancy values. Reducing the sampling times had minimal effect on pre- and post-treatment BP_{ND} in the striatal regions and thalamus (<2.5%) and the inferior temporal gyrus (<5%). The impact of shorter scan durations on occupancy values was also minimal (<2%) in all but the inferior temporal gyrus (6.11%). The variability observed here probably reflects the low signal to noise ratio of [^{18}F]fallypride binding in the temporal cortex and the additional impact of AD on D2/3 receptor density in this region (Joyce et al., 1998). The added effect of temporal volume loss is discussed below (see Limitations, Section 6.2.3).

In summary, the adapted [^{18}F]fallypride protocol, which uses interrupted scanning sessions, has shown high reproducibility and reliability in healthy older adults, and has proved tolerable in patients with AD. A post-treatment protocol has also been optimised, supporting the use of the adapted protocol for measuring D2/3 receptor occupancy in AD, and therefore fulfilling the aims of the current thesis.

6.2 Limitations

Specific limitations to each study are detailed in the relevant chapters, however several general limitations are discussed below.

6.2.1 Sampling

As with any research study, it is important to consider the sampling procedure, and the extent to which the study sample represents individuals with a particular condition within the general population. Selection bias did occur in Chapter 3, whereby the non-psychotic group were recruited from memory clinics, and the psychotic group from a mixture of memory clinics and community mental health teams. It is therefore possible that within the psychotic group, subjects differed in terms of global cognition and severity of psychotic symptoms, given that worsening of both infers referral to the community mental health teams. The purpose of this selection bias was to enhance recruitment of subjects experiencing psychotic symptoms and hence equalise group numbers. The recruitment procedure is unlikely

to have impacted on the current findings, given that MMSE was controlled for and all psychotic symptoms were below the threshold for antipsychotic treatment.

Issues regarding diagnostic accuracy should also be considered. All AD patients in the current study (Chapters 3 and 5) met the diagnosis for 'probable AD' following the NINCDS-ADRDA criteria (McKhann et al., 1984), and were excluded from the study if they presented with any symptoms of DLB or EPS. Screening measures were carried out on all healthy controls (Chapter 4), including the MMSE and an MRI scan, in order to rule out cognitive impairment and pathology indicative of dementia.

The sample size used in the neuropsychological testing component of the current thesis (Chapter 3) was based upon a power calculation, which took into account the results of a previous study where motor speed was found to be 11% higher in psychotic ($n = 7$) compared to non-psychotic ($n = 16$) subjects (Reeves et al., 2009). The power calculation demonstrated that a sample size of 50 in each group would be required to detect a between-group difference of 11% in mean motor speed, one of the hypothesis-driven tests. However, time restraints on the current study meant that a sample size of 34 in the psychotic and 36 in the non-psychotic group were recruited. The current sample size was large enough to detect a between-group difference of 13.6% in mean motor speed. A sample size of 34 in the psychotic group compares favourably with previous studies comparing psychotic and non-psychotic patients with AD, in which 70% of studies had a sample size of <30 in the psychotic group (based on studies reviewed by Reeves et al. 2012). However, whilst the current sample was sufficiently large to compare neuropsychological test performance between psychotic and non-psychotic groups as a whole, the number of subjects in each delusional subgroup was not large enough to adequately determine whether the delusional subgroups had distinct neuropsychological profiles. In addition, due to the small sample size within each subgroup, the current study was unable to determine the ability of the Incomplete Letters and RVP tasks to predict the odds of delusional subtypes in AD.

The sample size for the imaging components of the current thesis ($N = 8$) was comparable to a previous reliability study of [^{18}F]fallypride carried out in healthy young adults ($N = 6$) (Mukherjee et al., 2002), and is a standard sample size used to establish the test-retest error of PET radiotracers. However, in the AD sample

(Chapter 5), only six baseline scans were obtained, and two of these were unable to return for the post-treatment scan due to unrelated health problems. A further post-treatment scan was also removed from the analysis due to excessive head movement. This meant that data on only three post-treatment scans were available and used in the analysis. Therefore, the sample size was too small to determine meaningful D2/3 occupancy data in AD, but can still be used to demonstrate the feasibility and tolerability of the protocol in this clinical population. Recruitment of the AD group for the scanning component of this study (Chapter 5) proved particularly challenging due to several changes to prescribing practices of antipsychotic drugs in dementia. In particular, the National Dementia Strategy, which aimed to significantly reduce antipsychotic prescribing, led to a change in prescribing practice, which meant that patients referred to the study were frailer and more cognitively impaired than was originally anticipated. This led to substantial amendments being made to the protocol (reduction in scanning times and approval to obtain consent from carers/relatives) in order to adapt for the more severely impaired sample. Disease severity and frailty are also likely to have impacted on drop-out rates and the quality of data obtained.

6.2.2 Neuropsychological Test Measures

The choice of the two hypothesis-driven tests was based on demonstrated and postulated links with dopaminergic function. Whilst the choice of the RVP was advantageous as it had been previously adapted for use in AD (Jones et al., 1992), the results of the current logistic regression analysis suggest that additional visual processing demands of the task may have reduced its sensitivity as a measure of sustained attention, and therefore dopaminergic function. This may explain the inability of the RVP to independently predict psychotic symptoms in AD (logistic regression analysis). Furthermore, the dopaminergic contribution to SRT task performance has been questioned (Pullman et al., 1990), with some postulating that additional attentional demands required by the task may have masked any between-group differences in dopaminergic-controlled motor speed (Goodrich et al., 1989). Of the remaining tasks in the neuropsychological test battery, it is possible that some were too complex for the present AD sample. Specifically, nine subjects from the

psychotic group were unable to complete the Go/No-Go task. This may have been due to the speed of the task, or anxiety effects of using a computer.

Chapter 3 of the current study included a large number of neuropsychological tests in order to establish the neuropsychological profile of psychotic symptoms in AD. The large test battery inevitably involved a large number of statistical comparisons, and may therefore have increased the chance of type 1 errors occurring. However, stringent correction criteria were applied to the results to correct for multiple comparisons, including Bonferroni and Fisher's LSD adjustments, in addition to tests being grouped into cognitive domains to reduce the number of statistical comparisons. The logistic regression analysis is also not without limitations, and is particularly affected by high correlations among predictor variables. However, multicollinearity was assessed, and the highest correlation occurring between the predictor variables was <0.5 (Spearman's rho), implying that such effects are unlikely to have significantly impacted on the reliability of the model (see Appendix 7.4.6). In addition, the possibility that a third moderating variable may have affected the association between the independent variable and outcome variable cannot be excluded. For example, an unmeasured variable may have strengthened or weakened the relationship between the Incomplete Letters task and the psychotic group. However, the fact that age, years of education, and MMSE were controlled for in the current study will have reduced the effects of confounding variables on the present findings.

The NPI rating scale was used to determine the presence of psychotic and behavioural symptoms in AD (Chapters 3 and 5). A major limitation of this scale is the fact that it relies on the subjective ratings of a carer/relative. The ratings are therefore likely to be influenced by a number of factors, including the frequency of contact between the patient and carer, and the knowledge of the informant as to the different manifestations of psychotic symptoms in AD. In order to control for these factors as far as possible, the carer/relative who had the most frequent contact with the patient was asked to complete the rating scale, and a detailed explanation of each symptom, together with relevant examples, was given to the informant to help them to recognise the symptoms.

6.2.3 Image Analysis: MRI and Partial Volume Effects

In an attempt to further increase the feasibility of the protocol for use in cognitively impaired individuals, the current study chose not to utilise the subjects' MRI data for co-registration with PET data. This decision was based upon previous experience of imaging older adults with AD (Reeves et al., 2009; Reeves et al., 2005), in whom a multi scan approach is more challenging, and tolerability to confined spaces is generally poor. Instead, PET images were co-registered to a [¹⁸F]fallypride PET template, and then warped to specific atlases with predefined ROIs. This process was carried out using an automated procedure, similar to the approach previously used to quantify [¹¹C]raclopride BP_{ND} in people with AD (Reeves et al., 2009). This method has the advantage of removing any subjectivity in the placing of ROIs. However, the templates were derived from structural and functional imaging data on healthy young adults, and may therefore have led to inaccuracies in the warping process, particularly in the smaller, noisier regions, such as the anterior cingulate cortex (Chapter 4). However, the method of image analysis does not appear to have affected the pattern of reproducibility across other brain regions, as our findings are consistent with previously conducted test-retest studies which used the subject's MRI (Cropley et al., 2008) or PET-MR co-registered images (Mukherjee et al., 2002) to define ROIs.

In addition, the relatively poor spatial resolution of PET has always been a limitation in quantitative studies. Limited resolution results in loss of signal from small ROIs and can also cause contamination of the signal due to spillover of activity from a neighbouring region. Partial volume effects are enhanced with ageing due to the reduction in size of certain brain regions (Morris et al., 1999). Given our sample, the accuracy of tracer quantification is likely to have been affected, and may have contributed to the high test-retest variability in the anterior cingulate cortex (Chapter 4). In terms of the quantification of occupancy data, partial volume effects are likely to have impacted on values obtained from the inferior temporal gyrus (Chapter 5), given that atrophy is particularly marked in this region in AD (Scahill et al., 2002). These effects could have led to artefactually low occupancy values in this region. Therefore, the ability of the protocol to measure D2/3 occupancy in the inferior temporal gyrus in older people warrants further exploration, across different clinical populations.

The above methodological limitations are less important for within-subject study designs, but will need to be addressed to maximise the potential of the protocol for use in between-subject comparisons, or to correlate regional BP_{ND} with behavioural measures.

6.3 Implications of Findings and Directions for Future Research

6.3.1 Neuropsychological Test Battery

The psychotic group in the current study experienced mild, transient symptoms, which caused minimal disruption to everyday activities, and therefore did not require antipsychotic medication. The fact that cognitive differences were found in patients presenting with such mild psychotic symptoms suggests that the RVP and Incomplete Letters tasks could potentially act as cognitive markers of psychosis-proneness in AD.

Whilst the sensitivity of the RVP is likely due to its association with striatal dopaminergic function (Reeves et al., 2010), this may not be the case for the Incomplete Letters task, which is more likely to reflect underlying pathology in the ventral visual pathway (Mishkin et al., 1983). This could be investigated further by including additional tasks of visuoperception, rather than focusing solely on tasks associated with striatal dopaminergic function.

In fact, given that only one of the hypothesis-driven tasks in the current study was able to detect significant between-group differences (RVP not SRT), the suggestion that tasks linked to striatal dopaminergic function provide the most sensitive markers of psychosis in AD should be re-evaluated. One interpretation of the current findings is that cognitive tests associated with D2/3 receptor availability in the associative striatum (attention), rather than the sensorimotor striatum (motor function), may be more sensitive markers of psychosis in AD. This could be further explored by identifying tasks which are associated with D2/3 receptor availability in the associative striatum (caudate) and/or tasks associated with its functional connections - specifically the dorsolateral prefrontal cortex. Examples of such tasks include the Stroop Colour-Word Test (interference score) and Continuous Performance Test, respectively (Rezai et al., 1993; Volkow et al., 1998).

Another possible avenue for future research would be to explore whether paranoid and misidentification subtypes of delusions are underpinned by distinct neurochemical markers, or if the two groups have the same neurobiological underpinning, albeit with different intensities. Based on the present results, one hypothesis might be that both the paranoid and misidentification subtypes are underpinned by increases in striatal D2/3 receptor availability, with additional pathology in the ventral visual pathway in the misidentification subgroup. Cholinergic dysfunction has been implicated in visuoperceptual disturbances (reviewed by Collerton et al., 2005), and it could thus be argued that misidentification phenomena occur later in the AD course due to more marked cholinergic deficits. Dopaminergic dysfunction has also been reported to play a significant role in misidentification phenomena, but only in the presence of pre-existing cholinergic deficits (Collerton et al., 2005). Therefore, it may be the case that D2/3 receptor availability is increased along a continuum from mild increases in the persecutory group, through to more marked increases in the misidentification group. The heightened cholinergic/dopaminergic imbalance in this group could underlie the attentional and perceptual deficits observed. To explore this further, future research could investigate differences in dopaminergic and cholinergic function between the delusional subgroups. *In vivo* imaging of both neurotransmitters in regions along the ventral visual pathway, and its projections (limbic and frontal regions), could identify specific neurochemical markers of the different subtypes of psychotic symptoms, which could potentially influence future treatments. More marked cholinergic deficits together with heightened D2/3 receptor availability in the misidentification group could indicate a role for combined therapy in the treatment of misidentification phenomena, as shown by a previous study which used this approach to reduce hallucinations in AD (Bergman et al., 2003).

6.3.2 Imaging

The shorter scanning times required for the adapted [¹⁸F]fallypride protocol could help to advance research across a range of cognitively and neurologically impaired populations in which dopamine has been implicated, including patients with dementia, PD, movement disorders, and disorders of impulsivity.

A direct application of the current research is the use of the adapted [¹⁸F]fallypride protocol in a study which aims to explore the mechanisms underlying antipsychotic sensitivity in the elderly by combining data on drug dosage, plasma kinetics, D2/3 receptor occupancy, and symptom reduction in patients with AD and late-onset schizophrenia-like illness. The study aims to establish if there are disease-specific differences relating to pharmacokinetic and pharmacodynamic mechanisms of antipsychotic drug sensitivity within the two groups. Ultimately, the research could be used to inform and guide dosing strategies of the antipsychotic amisulpride, by establishing the minimal clinically effective dose of the drug, plus the optimal plasma levels and dose-occupancy range for response and avoidance of motor side effects. Subsequently, the work could be extended to other antipsychotic drugs and potentially in the development of new antipsychotics for use in the older population. This research, together with the work of Uchida et al. (2012) in older (but not late-onset) patients with schizophrenia, could transform the current attitudes towards antipsychotic prescribing in the elderly, meaning more patients are successfully treated for their psychotic and behavioural symptoms, enabling a better quality of life for both the patient and carer.

In addition to defining the ‘therapeutic window’ of striatal D2/3 occupancy, the protocol also has scope to explore the role of limbic D2/3 occupancy in antipsychotic response. Clinically relevant doses of amisulpride and other atypical antipsychotics have shown higher temporal and thalamic D2/3 receptor occupancy compared to striatal occupancy, and this limbic selectivity has been suggested to underpin the reduced side effect profile of the newer antipsychotics (Bressan et al., 2003; Xiberas et al., 2001b). Therefore the ability of the adapted [¹⁸F]fallypride protocol to image D2/3 receptor occupancy in these regions could advance the understanding of the therapeutic efficacy and low EPS profile of atypical antipsychotic drugs, and be influential to future drug development. However, it must be noted that the ability of the protocol to image D2/3 occupancy in the inferior temporal gyrus in AD warrants further exploration, given that occupancy values were very low in the current sample.

The high reliability of the adapted [¹⁸F]fallypride protocol means that it can be applied not only to D2/3 receptor occupancy studies, but also to image endogenous neurotransmission in striatal and limbic regions. A potential use for this paradigm

would be to explore dopamine release in psychotic versus non-psychotic individuals with AD. At present, research has focused on post-synaptic indices of dopamine function using single scan measures, which reflect both receptor density and levels of endogenous dopamine, making interpretation of the measure difficult (Laruelle 2000). Using the adapted [¹⁸F]fallypride protocol to measure dopamine release in psychotic compared to non-psychotic subjects, and in relation to specific neuropsychological tasks, could clarify the contribution of dopamine to psychosis and psychosis-subtypes.

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Appendix

7.1 Leaflets, Information Sheets and Consent Forms

(Font size 14 was used in the original documents)

7.1.1 Establishing the Neuropsychological Profile of Psychosis in Alzheimer's Disease

Summary Leaflet

Are you between 55 and 95 years of age? Do you have a memory problem? Are you interested in taking part in research?

We are looking to recruit 100 people who have memory problems to our study over the next 2 and a half years. Approximately half of the people we recruit will have had experiences that are difficult to explain - such as believing others have stolen from them - whereas the other half will not. We wish to find out whether tests known to be linked with a naturally produced brain chemical, dopamine, differ in people with memory problems who have unexplained experiences compared to those without.

Dopamine is a chemical which is produced naturally within the brain. In people with Alzheimer's disease, increased dopamine has been linked with unexplained experiences and has also been linked to both speed and the ability to maintain concentration.

Taking part will involve:

- (i) You will be asked to carry out a series of tests
- (ii) Your carer will be asked about any symptoms you may have

If differences in performance were found between people who have unexplained experiences and those who do not, this would help us to understand the underlying cause and develop a test battery to monitor the effects of drugs used to treat these symptoms, as such drugs act to reduce brain dopamine.

If you think you might be interested in taking part, please contact me on:

020 7848 0346 (office)

07930 278 810 (mobile)

Email: chloe.clark-papasavas@kcl.ac.uk

Thank you for taking the time to read this,

Chloe Clark-Papasavas, Institute of Psychiatry, Camberwell

Information Sheet

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with relatives, friends and your GP if you wish.

Why me?

You are aged between 55 and 95 years of age and have memory problems. Some of you will have been chosen because you have no other symptoms, and some of you will have had distressing experiences that are difficult to explain. For example, you may have wondered if things had been stolen from the house, or whether people were against you. You may have seen or heard things that no one else has, or you may not always recognise people that are familiar to you.

What is the Purpose of the Study?

This study will form the basis of a PhD student project and we are looking to recruit 100 people who have memory problems to our study over the next 2 and a half years. We wish to find out whether people with memory problems who have ‘unexplained experiences’ find it more or less difficult to do particular tests compared to people who have no such symptoms. The tests that we will ask you to do have been shown to be linked with a naturally produced chemical in the brain, dopamine. You may have heard about dopamine in relation to Parkinson’s disease, in which ‘too little’ dopamine is available in the brain. In people with memory problems, we have previously shown that unexplained experiences are more likely in people who have higher levels of dopamine in their brain. We also found that higher dopamine was linked with faster movement, but more difficulties in concentrating over several minutes. There were not enough people in this study to directly compare people with unexplained experiences to those without. This study aims to recruit a larger group of people with memory problems, to allow a direct comparison between groups of performance on a range of tests known to be linked with brain dopamine.

Why is it Important?

If we find that there are differences between the two groups in their performance on tests that are linked with brain dopamine, this would help us to understand more about the underlying cause of troublesome, unexplained experiences in people with memory problems. Our findings could also be used to develop a series of tests – a test battery – that could be used to monitor the effects of drug treatments that aim to reduce the frequency of occurrence of these experiences, as the drugs act to reduce brain dopamine.

Do I have to take part?

It is up to you to decide whether or not to take part. Take your time, discuss things with your carer/relative/doctor and ask us if there is anything that is not clear or if you would like more information. If you decide not to take part your treatment will not be affected by your decision. You are free to withdraw at any time without explanation and your future treatment will not be affected. If you do decide to take part you and your carer/relative will each be given a copy of this information sheet to keep and asked to sign a consent form. If you decide to take part you are still free to

withdraw at any time, without giving a reason, and this will not affect your future treatment. You will be given a copy of your signed consent form and we will inform your GP about your involvement in the project.

What will happen to me if I take part?

If you decide that you may want to take part in the study, one of the research team headed by Dr Suzanne Reeves will arrange a time to meet with you, to discuss the study in more detail and answer any questions you may have. Dr Reeves is a psychiatrist who specialises in treating older people with mental health and memory problems and, in addition to her research, she works as a Consultant Psychiatrist in North Southwark Community Mental Health Team for Older Adults. Chloe Clark-Papasavas is a student who will be carrying out the majority of the testing and interviewing you. Taking part will involve being interviewed at home and being asked to carry out a series of tests, all of which are brief and some of which involve the use of a touch screen computer. You will be given plenty of time to familiarise yourself with the touch screen. The total time involved should be less than an hour. Your carer will also be asked some questions about your well-being and how you have been getting on in the past few weeks, to see if you have been experiencing any troublesome symptoms.

What are the possible disadvantages and risks of taking part?

There are no risks involved. Taking part will of course mean giving up your time to be interviewed and assessed.

What are the possible benefits of taking part?

There will be no direct benefits to yourself.

What Happens When the Study Stops?

A letter will be sent to your doctor to inform him/her that you are no longer involved in the study.

What if something goes wrong?

If you have any problems, concerns, complaints or other questions about the study, you should contact Dr Reeves in the first instance. In the unlikely event of participants experiencing any serious adverse effects due to participation in the study, there are facilities for compensation in place, via the Institute of Psychiatry Professional Liability Insurance.

Will my taking part in this study be kept confidential?

We will inform your GP of your participation in the study and may also need to ask him or her some questions about your medical history. All information that is collected about you during the course of the research will be kept strictly confidential. Aside from the possibility of passing on any relevant information to your GP, information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

After the study has been completed, we would anticipate presenting the results and conclusions at scientific meetings (within months) and publishing them in a

scientific journal (within a year). You will not be identified within these. If you wish, a copy of any published article or report will be sent to you.

Who is organising and funding the research?

Guys and St Thomas Charity are funding the project.

Who has reviewed the study?

The committee for Guys and St Thomas Charity have sent the project for external review. The study has also been reviewed by the Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethics Committee

Contact for Further Information

Chloe Clark-Papasavas,
Department of Old Age Psychiatry, PO Box 070
Institute of Psychiatry, De Crespigny Park
London SE5 8AF

☎ 020 7848 0346;
07930 278 810 (mobile)
Email: chloe.clark-papasavas@kcl.ac.uk

Many thanks for your interest in the study,
Dr Suzanne Reeves, Professor Robert Howard (Head of Department)

Investigator's signature.....Date.....

(NAME IN BLOCK CAPITALS).....

Consent Form

The participant should complete the whole of this sheet him or herself.

Place a \surd in each of the boxes if the statement applies to you:

I have read the Information Sheet

I have been given the opportunity to ask questions and discuss this study.

I have received enough information about the study and satisfactory answers to all my questions.

I understand that a carer/relative will be asked to provide information about me

I agree to disclosure of my medical records to researchers

I understand that I am free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting future medical care.

I agree to take part in the study

I understand that my doctor will be informed if any of the results of the tests carried out as part of the research are important for my health.

The study has been explained to me by:
Prof/Dr/Mr/Mrs/Ms _____

Signed.....Date.....

(NAME IN BLOCK CAPITALS).....

Investigator's signature.....Date:

(NAME IN BLOCK CAPITALS).....

Please inform my GP that I am taking part in this study

7.1.2 Establishing the Reliability of [¹⁸F]-Fallypride Imaging in Healthy Older People

Summary leaflet

Are you between 55 and 95 years of age? Would you like to take part in research?

We are looking to recruit 8 healthy volunteers to take part in a study. Our aim is to establish the reliability of a brain scanning technique that measures a naturally produced brain chemical, dopamine. You may have heard about dopamine in relation to Parkinson's disease, where too little dopamine is produced. This type of brain scan is used in young people but involves long periods in the scanner (up to 2 hours at a stretch).

Our study aims to use a technique for measuring brain dopamine that has been specifically adapted to reduce the length of time spent in the scanner and we wish to find out how reliable it is. The best way of establishing the reliability of a measure is to find out how much it varies in the same person, from one occasion to the next. The more reliable the measure, the less variation there is.

Taking part will involve

- (i) Having an MRI scan
- (ii) Having 2 scans that measure dopamine in the brain

Once we have established the degree of variation in our measure between the 2 scanning sessions, we can use this to measure the action of drugs that act at dopamine sites in people with Alzheimer's disease, with the aim of reducing drug side effects.

If you think you might be interested in taking part, please contact me on 020 7848 0548 (office), 07947036513 (mobile), or email suzanne.j.reeves@kcl.ac.uk

Thank you for taking the time to read this,

Dr Suzanne Reeves, Institute of Psychiatry, Camberwell

Information Sheet

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with relatives, friends and your GP if you wish.

Why me?

You are aged between 55 and 95 years of age and are healthy.

What is the Purpose of the Study?

We wish to establish the reliability of a brain imaging technique that measures a naturally produced brain chemical, dopamine. The term ‘reliability’ describes how stable a measure is over time, and the more reliable a measure is, the less fluctuation there is in the measure. The best way of establishing the reliability of a measure is to measure the degree (percentage) of variability in the measure in the same person, from one occasion to the next. In young people, the measure of brain dopamine obtained using a particular imaging method has been shown to vary between 5% and 10%, depending upon the brain region examined. However, the method involves multiple and lengthy scanning sessions (up to 2 hours at a time over a total of 4 hours). We have adapted this technique to make it more feasible for use in older people, by reducing the length of time spent in the scanner and wish to find out how reliable our method is at measuring dopamine in several brain regions. We plan to do this by asking participants to have 2 brain scans that measure dopamine, 4 weeks apart, to find out the percentage variation in the measure between the 2 scanning sessions.

Why is it Important?

In young people, this type of imaging has been used to measure the action of drugs at brain dopamine sites and has helped to optimise drug dosage and treatment strategies, with the aim of reducing side effects. This area of research has been neglected in older people, particularly in people with dementia. If we find that our adapted protocol is easy to tolerate and can provide a reliable measure of dopamine, we can then utilise this to investigate the reasons why older people are more vulnerable to developing side effects following the use of drugs that act at dopamine sites. If we know the degree of variation inherent in our technique, we can determine the number of participants we would need to carry out such a study. We use statistical programmes to do these calculations. In addition, an imaging technique that has been specifically adapted to reduce the time spent in the scanner could be used in a wide range of clinical and research settings.

Do I have to take part?

It is up to you to decide whether or not to take part. Take your time, discuss things with your carer/relative/doctor and ask us if there is anything that is not clear or if you would like more information. You are free to withdraw at any time without explanation. If you do decide to take part you will be given a copy of this information sheet to keep and asked to sign a consent form. If you decide to take part you are still free to withdraw at any time, without giving a reason. You will be given

a copy of your signed consent form and we will inform your GP about your involvement in the project.

What will happen to me if I take part?

If you decide that you may want to take part in the study, Dr Suzanne Reeves, or one of the research team who is carrying out the research, will arrange a time to meet with you, to discuss the study in more detail and answer any questions you may have. Dr Reeves is a psychiatrist who specialises in treating older people with mental health and memory problems and, in addition to her research, she works as a Consultant Psychiatrist in North Southwark Community Mental Health Team for Older Adults. She has been carrying out imaging research in older people since 2003 and has been funded by the Guys and St Thomas' Charity to carry out her current project. Taking part will involve having 2 brain scans that measure dopamine sites.

1. First brain scan:

What Happens During the Brain Scan?

The brain scan will take place at St Thomas' Hospital. The type of brain scan you will be having is a PET scan. PET stands for positron emission tomography and is a scan which allows us to measure the amount of dopamine in the brain. If you would like to visit the Centre prior to deciding whether or not you wish to take part in the study, this can be arranged. Otherwise, we have some photographs of the scanner that we can show you. On the day of each scan, you will be transported to the Imaging Sciences Centre at St Thomas' Hospital in a minicab if you wish, or if you prefer you can make your own way there and we will reimburse your travel expenses. When you reach the unit, Dr Reeves or one of the research team will talk you through the scanning procedure, so that you can ask any questions. Before the scan a small tube (a cannula) will be placed into a vein in your arm, and a small amount of a chemical will be injected into the tube. This chemical allows us to measure dopamine in the brain. Once you are comfortable in the scanner, you will be asked to stay still for a 5 minute scan, to make sure you are positioned correctly. This will be followed by a series of scans lasting 30-40 minutes each with rest breaks in between, over a period of 4 hours. You will need to lie still in the scanner during each session, so that the pictures we take are not blurred. Your head will be supported by a moulded head-rest and a strap, to lessen the chance of your head moving without restricting it. The scanner is quiet and you can go to sleep if you wish. If you prefer to listen to music, there is a radio/cassette/CD player in the room. After 4 weeks, we will ask you to return for a second scan, which will be identical to the first one

Will I Need to Have Any Other Tests?

Yes, an MRI scan. We will arrange for you to have a scan that gives us a detailed picture of the structure of the brain. This will be performed at the Centre for Neuroimaging Sciences, based in Camberwell and jointly run by the Institute of Psychiatry and the South London and Maudsley NHS Foundation Trust. MRI stands for Magnetic Resonance Imaging and gives us a picture of your brain by using a powerful magnet. No radiation (X-Rays) is involved. You must not have a scan if you have received metal injuries to the eye, had metallic objects (including clips) inserted into your body at an operation, if you have received a shotgun or war injury,

or have a heart pacemaker. The radiographer will go through a list of possible risks with you before you go into the scanner. The scanner feels rather cramped inside and makes buzzing and whirring sounds, but will be over within around 15 minutes. This type of scan can help to diagnose memory problems that may be related to having had a stroke or a head injury. If we find out anything that is important for your doctor to know, we will pass this information on.

What are the possible disadvantages and risks of taking part?

PET scanning: This involves a small dose of radioactivity, which is given via an injection. Dr Reeves, or another suitably qualified practitioner will need to insert a small cannula into one of the veins in your arm to allow the injection to be given and this will be removed as soon as the scan is completed. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year and this varies depending upon where you live. This is referred to as background radiation. This research gives your body the equivalent of about 4 years of background radiation. The scans you will have if you take part in this study involve exposure to radiation. The additional amount of radiation involved is the same amount that everyone in the UK receives from natural sources over a period of about 4 years. In the general population, the chance of anybody getting a fatal cancer during their lifetime is roughly 1 in 5. The additional risk associated with the radiation in this study is up to approximately 1 in 2300. Taking part in this study will therefore increase your chance of getting a fatal cancer from an existing 1 in 5 up to at most 1 in 4.99.

During the study, you should let us know if you need to start any new treatments. Before each of the PET scans, you should not drink any alcohol for 24 hours. On the morning (or afternoon) of the PET scan, you should limit caffeine intake. If you have been exposed to radiation in the past year, either from medical investigations, or taking part in other research projects, you should not take part in the study. You will be given as much time as you need to discuss this with Dr Reeves.

What are the possible benefits of taking part?

There will be no direct benefits to yourself, but if we establish that the imaging technique is a reliable one – in other words if the measure varies little (< 20%) between the two scanning sessions - we will apply this protocol to a clinical setting, to examine the action of drugs that act at dopamine sites. We do reimburse you for your time with £40 per visit to the unit. We will of course provide transport and lunch or soft drinks that you may require. If you do not wish to accept payment for yourself, we would ask you to take the money and use it to benefit a charity of your choice. We can give you a picture of your PET scan at a later date if you would like this.

What Happens When the Study Stops?

A letter will be sent to your doctor to inform him/her that you are no longer involved in the study.

What if something goes wrong?

If you have any problems, concerns, complaints or other questions about the study, you should contact Dr Reeves in the first instance. In the unlikely event of participants experiencing any serious adverse effects due to participation in the

study, there are facilities for compensation in place, via the Institute of Psychiatry Professional Liability Insurance.

Will my taking part in this study be kept confidential?

We will inform your GP of your participation in the study and may also need to ask him or her some questions about your medical history. All information that is collected about you during the course of the research will be kept strictly confidential. Aside from the possibility of passing on any relevant information to your GP, information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

After the study has been completed, we would anticipate presenting the results and conclusions at scientific meetings (within months) and publishing them in a scientific journal (within a year). You will not be identified within these. If you wish, a copy of any published article or report will be sent to you.

Who is organising and funding the research?

Guys and St Thomas Charity are funding the project for 2 years.

Who has reviewed the study?

The committee for Guys and St Thomas Charity have sent the project for external review. The study has also been reviewed by the Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethics Committee

Contact for Further Information

Dr Suzanne Reeves,
Department of Old Age Psychiatry, PO Box 070
Institute of Psychiatry, De Crespigny Park
London SE5 8AF
☎ 020 7848 0548/0550, Fax 020 7848 0632 07947 036 513 (mobile)

Many thanks for your interest in the study, Dr Suzanne Reeves, Professor Robert Howard (Head of Department)

Investigator's signature.....Date.....

(NAME IN BLOCK CAPITALS).....

Consent Form

The participant should complete the whole of this sheet him or herself.

Place a \surd in each of the boxes if the statement applies to you:

I have read the Information Sheet

I have been given the opportunity to ask questions and discuss this study.

I have received enough information about the study and satisfactory answers to all my questions.

I understand that I am free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting future medical care.

I agree to disclosure of my medical records to researchers

I agree to take part in the study

I understand that my doctor will be informed if any of the results of the tests carried out as part of the research are important for my health.

The study has been explained to me by:
Prof/Dr/Mr/Mrs/Ms _____

Signed.....Date.....

(NAME IN BLOCK
CAPITALS).....

Investigator's signature.....Date.....

(NAME IN BLOCK
CAPITALS).....

Please inform my GP that I am taking part in this study

7.1.3 Imaging Dopamine Receptor Occupancy During Antipsychotic Treatment in Alzheimer's Disease

Summary Leaflet

Are you between 55 and 95 years of age? Have you been prescribed a medication to help with troublesome or distressing symptoms?

We are looking to recruit 8 people who have memory problems and who have been prescribed the drug amisulpride. We want find out which effects of the drug are linked with its action on a naturally produced brain chemical dopamine.

Dopamine is a chemical that helps to focus attention and co-ordinate movements. Amisulpride acts to reduce dopamine and, for this reason, may affect concentration or speed of movement.

In young people, brain scans have been used to find out the lowest possible dose of drugs like amisulpride that can be used to reduce symptoms without causing side effects and we would like to do the same in people with memory problems.

Taking part will involve:

- (i) Both you and your carer will be asked some questions before and after you begin drug treatment.
- (ii) Having 2 brain scans that measure dopamine sites in the brain – one before and one after 2-8 weeks of treatment.

If you think you might be interested in taking part, please contact me on 020 7848 0548 (office), 07947036513 (mobile), or email suzanne.j.reeves@kcl.ac.uk

Thank you for taking the time to read this,

Dr Suzanne Reeves, Institute of Psychiatry, Camberwell

Information Sheet

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with relatives, friends and your GP if you wish.

Why me?

Your doctor wishes to start you on medication to help with some of your symptoms. The name of the drug is amisulpride (Solian). Overall 8 people who are about to start this drug will be taking part in the study, which should take about a year to complete.

What is the Purpose of the Study?

We wish to find out more about the action of amisulpride in the brain, using a type of scan that measures a naturally produced chemical, dopamine. Dopamine is important in the brain as it helps us to co-ordinate movements and to concentrate on day to day events. You may have heard of it in relation to Parkinson's disease where people have too little available dopamine. Drugs like amisulpride act to reduce dopamine levels in the brain and are used because they can reduce troublesome or distressing symptoms in people with memory problems. By reducing dopamine they can however cause side effects, including stiffness of movement or tremor. In young people, brain scanning methods have been used to find out the lowest possible doses of drugs like amisulpride that can be used to treat symptoms without causing side effects. We would like to carry out a similar study in people with memory problems who are taking amisulpride. We want to see whether or not changes in dopamine that occur as a result of your treatment are linked with changes in the symptoms you experience, your ability to concentrate and side effects. The study will also form part of a PhD student project.

Why is it Important?

The research will provide us with valuable information about whether the effects of drugs like amisulpride are linked with their action on brain dopamine and will be used to inform a wider study that aims to investigate the reasons why older people are more sensitive to drug side effects than younger ones.

Do I have to take part?

It is up to you to decide whether or not to take part. Take your time, discuss things with your carer/relative/doctor and ask us about anything that is not clear or if you would like more information. If you decide not to take part your treatment will not be affected by your decision. You are free to withdraw at any time without explanation and your subsequent treatment will not be affected. If you do decide to take part you and your carer/relative will each be given a copy of this information sheet to keep and asked to sign a consent form. If you decide to take part you are still free to withdraw at any time, without giving a reason, and this will not affect your subsequent treatment. You will be given a copy of your signed consent form and we will inform your GP about your involvement in the project.

What will happen to me if I take part?

If you decide that you may want to take part in the study, Dr Suzanne Reeves, or one of the research team who is carrying out the research, will arrange a time to meet with you and your carer, to discuss the study in more detail and answer any questions you may have. Dr Reeves is a psychiatrist who specialises in treating older people with mental health and memory problems and, in addition to her research, she works as a Consultant Psychiatrist in North Southwark Community Mental Health Team for Older Adults. She has been funded by the Guys and St Thomas' Charity to carry out the research. She will not be prescribing your treatment, but will be in close contact with the doctor and/or team who are responsible for your clinical care and may need to access to your medical notes, for the purposes of her research. Taking part will involve several stages:

The research will involve both you and your carer being interviewed before and after starting amisulpride, so that we can see how effective the medication has been and monitor any side effects that you may experience. We will also ask you to have 2 brain scans, which will allow us to measure the action of amisulpride at dopamine sites.

1. **First Assessment:** Dr Reeves or one of her team will review your symptoms and check for any side effects. Your carer will be asked how you have been getting on in the past few weeks, to see if there have been any symptoms that are distressing you.
2. **First brain scan:** This will happen at St Thomas' Hospital before you start taking amisulpride medication. Dr Reeves will organise this as soon as possible after meeting with you, so that your treatment will not be delayed by you agreeing to take part in the study.

What Happens During the Brain Scan?

The type of brain scan you will be having is a PET scan. PET stands for positron emission tomography and is a scan which allows us to measure the amount of dopamine in the brain. By scanning you before and after treatment with amisulpride, we can see how much dopamine activity is reduced by the drug in different areas of the brain. This type of scan does not provide a detailed picture of the brain and will not help us to find out the cause of your memory problems. If you would like to visit the Centre prior to deciding whether or not you wish to take part in the study, this can be arranged. Otherwise, we have some photographs of the scanner that we can show you.

On the day of each scan, you and your carer will be transported to the Imaging Sciences Centre at St Thomas' Hospital in a minicab. When you reach the unit, Dr Reeves or one of the research team will talk you through the scanning procedure, so that you can ask any questions. Before the scan a small tube (a cannula) will be placed into a vein in your arm, and a small amount of a chemical will be injected into the tube. This chemical allows us to measure dopamine in the brain. Once you are comfortable in the scanner, you will be asked to stay still for a 5 minute scan, to make sure you are positioned correctly. This will be followed by a series of scans lasting 30 minutes each with rest breaks in between, over a period of 4 hours. You will need to lie still in the scanner during each session, so that the pictures we take are not blurred. Your head will be supported by a moulded head-rest and a strap, to lessen the chance of your head moving without restricting it. The scanner is quiet

and you can go to sleep if you wish. If you prefer to listen to music, there is a radio/cassette/CD player in the room.

3. **Second brain scan:** This will happen around 4 weeks after the first scan, and will follow a similar procedure. This time, there will be three scans with rest breaks in between, lasting a total of 2 and a half hours. The first two scans will last 20 minutes each, and the final scan will last 40minutes.

What are the possible disadvantages and risks of taking part?

PET scanning: This involves a small dose of radioactivity, which is given via an injection. Dr Reeves, or another suitably qualified practitioner will need to insert a small cannula into one of the veins in your arm to allow the injection to be given and this will be removed as soon as the scan is completed. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year and this varies depending upon where you live. This is referred to as background radiation. This research gives your body the equivalent of about 4 years of background radiation. The scans you will have if you take part in this study involve exposure to radiation. The additional amount of radiation involved is the same amount that everyone in the UK receives from natural sources over a period of about 4 years. In the general population, the chance of anybody getting a fatal cancer during their lifetime is roughly 1 in 5. The additional risk associated with the radiation in this study is up to approximately 1 in 2300. Taking part in this study will therefore increase your chance of getting a fatal cancer from an existing 1 in 5 up to at most 1 in 4.99

During the study, you should let us know if you need to start any new treatments. Before each of the PET scans, you should not drink any alcohol for 24 hours. On the morning (or afternoon) of the PET scan, you should limit caffeine intake. If you have been exposed to radiation in the past year, either from medical investigations, or taking part in other research projects, you should not take part in the study. You will be given as much time as you need to discuss this with Dr Reeves or one of her research team.

What are the possible benefits of taking part?

There will be no direct benefits to yourself, but the knowledge gained will be put to use to inform a wider study that aims to investigate the causes of antipsychotic drug sensitivity in older people.

We do reimburse you for your time with £40 per visit to the unit. We will of course provide transport and lunch or soft drinks that you may require. If you do not wish to accept payment for yourself, we would ask you to take the money and use it to benefit a charity of your choice. We can give you a picture of your PET scan at a later date if you would like this.

What Happens When the Study Stops?

Dr Reeves will not be involved in your treatment at any stage of the study, but will be in close contact with the doctor who is prescribing your medication. When the final assessment has been carried out, a letter will be sent to your doctor to inform him/her that you are no longer involved in the study.

What if something goes wrong?

If you have any problems, concerns, complaints or other questions about the study, you should contact Dr Reeves in the first instance. In the unlikely event of participants experiencing any serious adverse effects due to participation in the study, there are facilities for compensation in place, via the Institute of Psychiatry Professional Liability Insurance

Will my taking part in this study be kept confidential?

We will inform your GP of your participation in the study and may also need to ask him or her some questions about your medical history. All information that is collected about you during the course of the research will be kept strictly confidential. Aside from the possibility of passing on any relevant information to your GP, information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

After the study has been completed, we would anticipate presenting the results and conclusions at scientific meetings (within months) and publishing them in a scientific journal (within a year). You will not be identified within these. If you wish, a copy of any published article or report will be sent to you.

Who is organising and funding the research?

Guys and St Thomas Charity are funding the project for 2 years.

Who has reviewed the study?

The committee for Guys and St Thomas Charity have sent the project for external review. The study has also been reviewed by the Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethics Committee

Contact for Further Information

Dr Suzanne Reeves,
Department of Old Age Psychiatry, PO Box 070
Institute of Psychiatry, De Crespigny Park
London SE5 8AF

☎ 020 7848 0548/0550, Fax 020 7848 0632 07947 036 513 (mobile)

Many thanks for your interest in the study,
Dr Suzanne Reeves, Professor Robert Howard (Head of Department)

Investigator’s signature.....Date.....

(NAME IN BLOCK CAPITALS).....

.

Consent Form

The participant should complete the whole of this sheet him or herself.

Place a \surd in each of the boxes if the statement applies to you:

I have read the Information Sheet

I have been given the opportunity to ask questions and discuss this study

I have received enough information about the study and satisfactory answers to all my questions

I understand that a carer/relative will be asked to provide information about me

I agree to disclosure of my medical records to researchers

I understand that I am free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting future medical care

I agree to take part in the study

I understand that my doctor will be informed if any of the results of the tests carried out as part of the research are important for my health

The study has been explained to me by:
Prof/Dr/Mr/Mrs/Ms _____

Signed.....Date.....

(NAME IN BLOCK CAPITALS).....

Investigator's signature.....Date:

(NAME IN BLOCK CAPITALS).....

..

Please inform my GP that I am taking part in this study

7.2 Ethical Approval



National Research Ethics Service

South East London Research Ethics Committee (REC) 4
(Formerly known as The Joint South London and Maudsley and Institute of Psychiatry
Research Ethics Committee)
1st Floor, Camberwell Building
94 Denmark Hill
London
SE5 9RS

Telephone: 020 3299 5033
Facsimile: 020 3299 5085

24 September 2010

Dr Suzanne Reeves
Clinical Senior Lecturer in Old Age Psychiatry
Institute of Psychiatry
De Crespigny Park
London
SE5 8AF

Dear Dr Reeves

Study Title: **Characterising the Neuropsychological Profile and
Imaging Dopamine D2/3 receptor Occupancy During
Antipsychotic Treatment in Alzheimer's disease**

REC reference number: **10/H0807/75**

Thank you for your letter of 17 September 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has 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.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The favourable opinion applies to the following research site(s):

Research Site	Principal Investigator / Local Collaborator
Institute of Psychiatry	Dr Suzanne Reeves

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

This Research Ethics Committee is an advisory committee to London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research (“R&D approval”) should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation’s involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

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).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Investigator CV	1	22 July 2010
Protocol	1	15 July 2010
CV: Chloe Clark - Papasavas	1	22 July 2010
Letter of Invitation: Feasibility Study	1	15 July 2010
GP Letter: Feasibility Study	1	15 July 2010
Leaflet: Neuropsychological Profile	2	15 September 2010
REC application	3.0	15 July 2010
Covering Letter	1	15 July 2010
Covering Letter		17 September 2010
Letter from Sponsor	1	01 March 2010
Letter of invitation to participant	1	15 July 2010
GP/Consultant Information Sheets	1	15 July 2010
GP/Consultant Information Sheets	2	15 September 2010
Participant Information Sheet: Neuropsychological Profile	2	15 September 2010
Response to Request for Further Information		17 September 2010
Participant Information Sheet: Feasibility Study	1	15 July 2010
Participant Information Sheet: Pilot Study	2	15 September 2010
Participant Information Sheet: Reliability Study	2	15 September 2010
Participant Consent Form: Neuropsychological Profile	2	15 September 2010
Participant Consent Form: Feasibility Study	1	15 July 2010
Participant Consent Form: Pilot Study	2	15 September 2010
Participant Consent Form: Reliability Study	2	15 September 2010
Letter of Invitation: Neuropsychological Profile	1	15 July 2010
GP Letter: Neuropsychological Profile	1	15 July 2010
Leaflet: Reliability Study	2	15 September 2010

Leaflet: Pilot Study	2	15 September 2010
Evidence of insurance or indemnity	1	01 September 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

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
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

Please quote this number on all correspondence: 10/H0807/75

Yours sincerely



ff Mr Tony Eaton
Chair

Email: audrey.adams@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Jenny Liebscher
R&D office for NHS care organisation at lead site

7.2.1 Substantial Amendment 1



National Research Ethics Service NRES Committee London - Camberwell St Giles

(Formerly known as The Joint South London and Maudsley and Institute of Psychiatry
Research Ethics Committee)
Administrative address: Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Tel: 01223 597509
Fax: 01223 597645

07 July 2011

Dr Suzanne Reeves
Clinical Senior Lecturer in Old Age Psychiatry
Institute of Psychiatry
Institute of Psychiatry
De Crespigny Park
Camberwell
SE58AF

Dear Dr Reeves

Study title: Characterising the Neuropsychological Profile and
Imaging Dopamine D2/3 receptor Occupancy During
Antipsychotic Treatment in Alzheimer's disease
REC reference: 10/H0807/75
Amendment number: Amendment 1
Amendment date: 19 April 2011

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Consent Form: Consultee	1	19 April 2011
Protocol	2	19 April 2011
Notice of Substantial Amendment (non-CTIMPs)	Amendment 1	19 April 2011
Covering Letter : from Dr Suzanne Reeves		19 April 2011
e-mail from Dr Reeves, providing documents (NB originally handed in on 19 April, but it appears they have been mislaidd)		04 July 2011

This Research Ethics Committee is an advisory committee to the East of England Strategic Health Authority
*The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England*

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

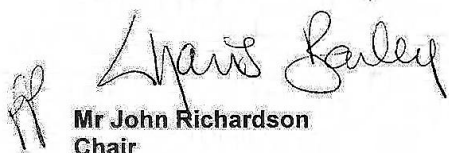
Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

10/H0807/75:

Please quote this number on all correspondence

Yours sincerely


Mr John Richardson
Chair

E-mail: charis.bailey@eoe.nhs.uk

Encs: List of names and professions of members who took part in the review

CC: Mrs Jenny Liebscher
Research and Development Office,
King's College, University of London
Institute of Psychiatry / South London and Maudsley NHS Foundation Trust
De Crespigny Park
London
SE5 8AF

This Research Ethics Committee is an advisory committee to East of England Strategic Health Authority
*The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England*

7.2.2 Substantial Amendment 2



Health Research Authority

NRES Committee London - Camberwell St Giles

(Formerly known as The Joint South London and Maudsley and Institute of Psychiatry
Research Ethics Committee)
Administrative address: Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Tel: 01223 597509
Fax: 01223 597645

17 April 2012

Dr Suzanne Reeves
Clinical Senior Lecturer in Old Age Psychiatry
Institute of Psychiatry
Institute of Psychiatry
De Crespigny Park
Camberwell
SE58AF

Dear Dr Reeves

Study title: Characterising the Neuropsychological Profile and Imaging Dopamine D2/3 receptor Occupancy During Antipsychotic Treatment in Alzheimer's disease
REC reference: 10/H0807/75
Amendment number: Amendment 2_030412
Amendment date: 03 April 2012
Amendment summary: Change to post-treatment scanning protocol from a 2-scan to a 3-scan approach for participants who are unlikely to tolerate scanning sessions longer than 40 minutes.

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Information Sheet: Pilot study	3	03 April 2012
Protocol	3	03 April 2012
Notice of Substantial Amendment (non-CTIMPs)	Amendment 2_030412	03 April 2012
Covering Letter : from Dr Suzanne Reeves		03 April 2012
e-mail from Jenny Liebscher (SLaM IoP R&D Office) confirming approval of this amendment		05 April 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

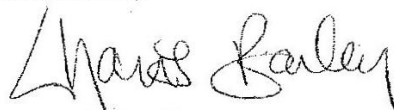
All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

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.

10/H0807/75:	Please quote this number on all correspondence
---------------------	---

Yours sincerely



Mr John Richardson
Chair

E-mail: charis.bailey@eoe.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy:

Mrs Jenny Liebscher
Research and Development Office,
King's College, University of London
Institute of Psychiatry / South London and Maudsley NHS Foundation Trust
De Crespigny Park
London
SE5 8AF

7.3 Modified version of the NPI

NPI rated by professional care NPI rated by friend/relative

"I am now going to ask you some questions designed to evaluate [subject's] behaviour. They can usually be answered 'yes' or 'no'."

A. Delusions

"Has [subject] had 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."

Yes No If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

- | | | Yes | No |
|----|--|--------------------------|--------------------------|
| 1. | Does the patient believe that he/she is in danger - or that others are planning to hurt him/her? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. | Does the patient believe that others are stealing from him/her? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. | Does the patient believe that his/her spouse is having an affair? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. | Does the patient believe that unwelcome guests are living in his/her house? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. | Does the patient believe that his/her spouse or others are not who they claim to be? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. | Does the patient believe that his/her house is not his/her home? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. | Does the patient believe that family members plan to abandon him/her? | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. | Does the patient believe that television or magazine figures are actually present in the home?
(Does he/she try to talk or interact with them?) | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. | Does the patient believe any other unusual things that I haven't asked about? | <input type="checkbox"/> | <input type="checkbox"/> |

"When were these behaviours at their worst?"

- | | |
|--|--------------------------|
| In the last month / Now as bad as ever | <input type="checkbox"/> |
| 1-6 months ago | <input type="checkbox"/> |
| 6 months-1 year ago | <input type="checkbox"/> |
| 1 year - 3 years ago | <input type="checkbox"/> |
| More than 3 years ago | <input type="checkbox"/> |

"Do they still occur?"

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>
"If no, when did they last occur?" (in months)	
<input style="width: 80px; height: 25px;" type="text"/>	

If the screening question is confirmed, determine the frequency and severity of the delusions.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst would you say they were mild moderate or severe?"

Severity

- | | | |
|-------------|--|--------------------------|
| 1. Mild | Delusions present but seem harmless and produce little distress in the patient | <input type="checkbox"/> |
| 2. Moderate | Delusions are distressing and disruptive | <input type="checkbox"/> |
| 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.) | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

B. Hallucinations

"Has [subject] had hallucinations such as false visions or voices? Has he/she seemed 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 patient actually has abnormal experiences of sounds or visions"

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

- | | | Yes | No |
|----|--|--------------------------|--------------------------|
| 1. | Does the patient describe hearing voices or act as if he/she hears voices? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. | Does the patient talk to people who are not there? | <input type="checkbox"/> | <input type="checkbox"/> |
| 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.)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. | Does the patient report smelling odours not smelled by others? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. | Does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. | Does the patient describe tastes that are without any known cause? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. | Does the patient describe any other unusual sensory experiences? | <input type="checkbox"/> | <input type="checkbox"/> |

"When were these behaviours at their worst?"

- | | |
|--|--------------------------|
| In the last month / Now as bad as ever | <input type="checkbox"/> |
| 1-6 months ago | <input type="checkbox"/> |
| 6 months-1 year ago | <input type="checkbox"/> |
| 1 year - 3 years ago | <input type="checkbox"/> |
| More than 3 years ago | <input type="checkbox"/> |

"Do they still occur?"

Yes No

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst would you say they were mild moderate or severe?"

Severity

- | | | |
|-------------|---|--------------------------|
| 1. Mild | Hallucinations present but seem harmless and produce little distress in the patient | <input type="checkbox"/> |
| 2. Moderate | Hallucinations are distressing and disruptive | <input type="checkbox"/> |
| 3. Marked | Hallucinations are very disruptive and are a major source of behavioural disruption.
(PRN medications may be prescribed to control them) | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

C. Agitation/Aggression

"Has the patient had periods when he/she refused to co-operate or wouldn't let people help him/her? Has he/she been hard to handle?"

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

		Yes	No
1.	Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes?	<input type="checkbox"/>	<input type="checkbox"/>
2.	Is the patient stubborn, having to have things his/her way?	<input type="checkbox"/>	<input type="checkbox"/>
3.	Is the patient uncooperative, resistive to help from others?	<input type="checkbox"/>	<input type="checkbox"/>
4.	Does the patient have any other behaviours that make him hard to handle?	<input type="checkbox"/>	<input type="checkbox"/>
5.	Does the patient shout or curse angrily?	<input type="checkbox"/>	<input type="checkbox"/>
6.	Does the patient slam doors, kick furniture, throw things?	<input type="checkbox"/>	<input type="checkbox"/>
7.	Does the patient attempt to hurt or hit others?	<input type="checkbox"/>	<input type="checkbox"/>
8.	Does the patient have any other aggressive or agitated behaviours?	<input type="checkbox"/>	<input type="checkbox"/>

"When were these behaviours at their worst?"

"Do they still occur?"

In the last month/ Now as bad as ever

1-6 months ago

6 months-1 year ago

1 year - 3 years ago

More than 3 years ago

Yes No

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the agitation/aggression.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst, would you say they were mild moderate or severe?"

Severity

- | | | |
|-------------|---|--------------------------|
| 1. Mild | Behaviour is disruptive but can be managed with redirection or reassurance | <input type="checkbox"/> |
| 2. Moderate | Behaviours disruptive and difficult to redirect or control | <input type="checkbox"/> |
| 3. Marked | Agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

D. Depression/Dysphoria

"Has the patient seemed sad or depressed? Has he/she said that he/she felt sad or depressed?"

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

- | | | Yes | No |
|----|--|--------------------------|--------------------------|
| 1. | Does the patient have periods of tearfulness or sobbing that seems to indicate sadness? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. | Does the patient say or act as if he/she is sad or in low spirits? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. | Does the patient put him/herself down or say that he/she feels like a failure? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. | Does the patient say that he/she is a bad person or deserves to be punished? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. | Does the patient seem very discouraged or say that he/she has no future? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. | Does the patient say that he/she is a burden to the family or that the family would be better off without him/her? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. | Does the patient express a wish for death or talk about killing him/herself? | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. | Does the patient show any other signs of depression or sadness? | <input type="checkbox"/> | <input type="checkbox"/> |

"When were these behaviours at their worst?"

"Do they still occur?"

- In the last month / Now as bad as ever
- 1-6 months ago
- 6 months-1 year ago
- 1 year - 3 years ago
- More than 3 years ago

Yes No

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the depression.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst, would you say they were mild moderate or severe ?"

Severity

- | | | |
|-------------|---|--------------------------|
| 1. Mild | Depression is distressing but usually responds to redirection or reassurance | <input type="checkbox"/> |
| 2. Moderate | Depression is distressing, depressive symptoms are spontaneously voiced by the patient and difficult to alleviate | <input type="checkbox"/> |
| 3. Marked | Depression is very distressing and a major source of suffering for the patient | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

E. Anxiety

"Has the patient been very nervous, worried or frightened for no apparent reason? Has he/she seemed very tense or fidgety? Has the patient been afraid to be apart from you?"

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

		Yes	No
1.	Does the patient say that he/she is worried about planned events?	<input type="checkbox"/>	<input type="checkbox"/>
2.	Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense?	<input type="checkbox"/>	<input type="checkbox"/>
3.	Does the patient have periods of (or complain of) shortness of breath, gasping, or sighing for no apparent reason other than nervousness?	<input type="checkbox"/>	<input type="checkbox"/>
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).	<input type="checkbox"/>	<input type="checkbox"/>
5.	Does the patient avoid certain places or situations that makes him/her more nervous such as riding in the car, meeting with friends, or being in crowds?	<input type="checkbox"/>	<input type="checkbox"/>
6.	Does the patient become nervous and upset when separated from you (or his/her caregiver)? (Does he/she cling to you to stop you being separated?)	<input type="checkbox"/>	<input type="checkbox"/>
7.	Does the patient show any other signs of anxiety?	<input type="checkbox"/>	<input type="checkbox"/>

"When were these behaviours at their worst?"

"Do they still occur?"

In the last month /Now as bad as ever

1-6 months ago

6 months-1 year ago

1 year - 3 years ago

More than 3 years ago

Yes No

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the anxiety.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst would you say they were mild moderate or severe ?"

Severity

- | | | |
|-------------|---|--------------------------|
| 1. Mild | Anxiety is distressing but usually responds to redirection or reassurance | <input type="checkbox"/> |
| 2. Moderate | Anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate | <input type="checkbox"/> |
| 3. Marked | Anxiety is very distressing and a major source of suffering for the patient | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

F. Elation/Euphoria

"Has the patient seemed too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents or spending time with family members. I am asking if the patient has a persistent and abnormally good mood or finds humour where others do not."

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

		Yes	No
1.	Does the patient appear to feel too good or to be too happy, different from his/her usual self?	<input type="checkbox"/>	<input type="checkbox"/>
2.	Does the patient find humour and laugh at things that others do not find funny?	<input type="checkbox"/>	<input type="checkbox"/>
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 happened to others)?	<input type="checkbox"/>	<input type="checkbox"/>
4.	Does the patient tell jokes or make remarks that have little humour for others but seem funny to him/her?	<input type="checkbox"/>	<input type="checkbox"/>
5.	Does he/she play childish pranks such as pinching or playing "hide and seek" for the fun of it?	<input type="checkbox"/>	<input type="checkbox"/>
6.	Does the patient "talk big" or claim to have more abilities or wealth than is true?	<input type="checkbox"/>	<input type="checkbox"/>
7.	Does the patient show any other signs of feeling too good or being too happy?	<input type="checkbox"/>	<input type="checkbox"/>

"When were these behaviours at their worst?"

"Do they still occur?"

In the last month / Now as bad as ever

1-6 months ago

6 months-1 year ago

1 year - 3 years ago

More than 3 years ago

Yes No

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the elation / euphoria.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst, would you say they were mild moderate or severe?"

Severity

- | | | |
|-------------|--|--------------------------|
| 1. Mild | Elation is notable to friends and family but is not disruptive | <input type="checkbox"/> |
| 2. Moderate | Elation is notably abnormal | <input type="checkbox"/> |
| 3. Marked | Elation is very pronounced, patient is euphoric and finds nearly everything to be humorous | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

G. Apathy/Indifference

"Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or lack motivation for starting new activities? Has he/she been more difficult to engage in conversation or in doing chores? Has the patient been apathetic or indifferent?"

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

- | | | Yes | No |
|----|--|--------------------------|--------------------------|
| 1. | Does the patient seem less spontaneous and less active than usual? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. | Is the patient less likely to initiate a conversation? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. | Is the patient less affectionate or lacking in emotions when compared to his/her usual self? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. | Does the patient contribute less to household chores? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. | Does the patient seem less interested in the activities and plans of others? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. | Has the patient lost interest in friends and family members? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. | Is the patient less enthusiastic about his/her usual interests? | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. | Does the patient show any other signs that he/she doesn't care about doing new things? | <input type="checkbox"/> | <input type="checkbox"/> |

"When were these behaviours at their worst?"

"Do they still occur?"

- In the last month / Now as bad as ever
- 1-6 months ago
- 6 months-1 year ago
- 1 year - 3 years ago
- More than 3 years ago

Yes No

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst, would you say they were mild moderate or severe?"

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 | <input type="checkbox"/> |
| 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 | <input type="checkbox"/> |
| 3. Marked | apathy is very evident and usually fails to respond to any encouragement or external events | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

H. Disinhibition

"Has the patient seemed to act impulsively without thinking? Has he/she said or done things that are not usually done or said in public? Has he/she done things that were embarrassing to you or others?"

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

- | | | Yes | No |
|----|--|--------------------------|--------------------------|
| 1. | Does the patient act impulsively without appearing to consider the consequences? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. | Does the patient talk to total strangers as if he/she knew them? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. | Does the patient say things to people that are insensitive or hurt their feelings? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. | Does the patient say crude things or make sexual remarks that they would not usually have said? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. | Does the patient talk openly about very personal or private matters not usually discussed in public? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. | Does the patient take liberties or touch or hug others that is out of character for him/her? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. | Does the patient show any other sign of loss of control of his/her impulses? | <input type="checkbox"/> | <input type="checkbox"/> |

"When were these behaviours at their worst?"

"Do they still occur?"

- In the last month / Now as bad as ever
- 1-6 months ago
- 6 months-1 year ago
- 1 year - 3 years ago
- More than 3 years ago

Yes No

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst, would you say they were mild moderate or severe?"

Severity

- | | | |
|-------------|--|--------------------------|
| 1. Mild | Disinhibition is notable but usually responds to redirection and guidance | <input type="checkbox"/> |
| 2. Moderate | Disinhibition is very evident and difficult to overcome by the caregiver | <input type="checkbox"/> |
| 3. Marked | Disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

I. Irritability/Lability

"Has the patient got irritated and easily disturbed? Have his/her moods been very changeable? Has he/she been 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 had abnormal irritability, impatience, or rapid emotional changes different from his/her usual self."

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

- | | | Yes | No |
|----|--|--------------------------|--------------------------|
| 1. | Does the patient have a bad temper, flying "off the handle" easily over little things? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. | Does the patient rapidly change moods from one to the other, being fine one minute and angry the next? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. | Does the patient have sudden flashes of anger? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. | Is the patient impatient, having trouble coping with delays or waiting for planned activities? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. | Is the patient cranky and irritable? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. | Is the patient argumentative and difficult to get along with? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. | Does the patient show any other signs of irritability? | <input type="checkbox"/> | <input type="checkbox"/> |

"When were these behaviours at their worst?"

"Do they still occur?"

- | | |
|--|--------------------------|
| In the last month / Now as bad as ever | <input type="checkbox"/> |
| 1-6 months ago | <input type="checkbox"/> |
| 6 months-1 year ago | <input type="checkbox"/> |
| 1 year - 3 years ago | <input type="checkbox"/> |
| More than 3 years ago | <input type="checkbox"/> |

Yes No

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the irritability.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst would you say they were mild moderate or severe?"

Severity

- | | | |
|-------------|---|--------------------------|
| 1. Mild | Irritability or lability is notable but usually responds to redirection and guidance | <input type="checkbox"/> |
| 2. Moderate | Irritability and lability are very evident and difficult to overcome by the caregiver | <input type="checkbox"/> |
| 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 | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

J. Aberrant Motor Behaviour

"Has the patient been pacing, doing things over and over such as opening closets or drawers, or been repeatedly picking at things or winding string or threads?"

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

- | | | Yes | No |
|----|---|--------------------------|--------------------------|
| 1. | Does the patient pace around the house without apparent purpose? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. | Does the patient rummage around opening and unpacking drawers or closets? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. | Does the patient repeatedly put on and take off clothing? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. | Does the patient have repetitive activities or "habits" that he/she performs over and over? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. | Does the patient engage in repetitive activities such as handling buttons, picking, wrapping string etc.? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. | Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. | Does the patient do any other activities over and over? | <input type="checkbox"/> | <input type="checkbox"/> |

"When were these behaviours at their worst?"

- In the last month / Now as bad as ever
- 1-6 months ago
- 6 months-1 year ago
- 1 year - 3 years ago
- More than 3 years ago

"Do they still occur?"

Yes No

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the motor behaviours.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst, would you say they were mild moderate or severe?"

Severity

- | | | |
|-------------|---|--------------------------|
| 1. Mild | Abnormal motor activity is notable but produces little interference with daily routines | <input type="checkbox"/> |
| 2. Moderate | Abnormal motor activity | <input type="checkbox"/> |
| 3. Marked | Abnormal motor activity is very evident, it usually fails to respond to any intervention by the caregiver and is a major source of distress | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour/ did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

K. Sleep

"Has the patient had 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)? Has he/she been up at night? Has he/she wandered at night, got dressed or disturbed your sleep?"

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

- | | | Yes | No |
|----|--|--------------------------|--------------------------|
| 1. | Does the patient have difficulty falling asleep? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. | Does the patient get up during the night (do not count if the patient gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. | Does the patient wander, pace or get involved in inappropriate activities at night? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. | Does the patient awaken you during the night? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. | Does the patient awaken at night, dress, and plan to go out thinking that it is morning and time to start the day? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. | Does the patient awaken too early in the morning (earlier than was his/her habit)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. | Does the patient sleep excessively during the day? | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. | Does the patient have any other night-time behaviours that bother you that we haven't talked about? | <input type="checkbox"/> | <input type="checkbox"/> |

"When were these behaviours at their worst?"

"Do they still occur?"

- In the last month / Now as bad as ever
- 1-6 months ago
- 6 months-1 year ago
- 1 year - 3 years ago
- More than 3 years ago

- Yes No
-

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the sleeplessness.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- | | | |
|----|---|--------------------------|
| 1. | Occasionally - less than once per week | <input type="checkbox"/> |
| 2. | Often - about once per week | <input type="checkbox"/> |
| 3. | Frequently - several times per week but less than every day | <input type="checkbox"/> |
| 4. | Very frequently - once or more per day | <input type="checkbox"/> |

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst would you say they were mild moderate or severe ?"

Severity

- | | | |
|-------------|--|--------------------------|
| 1. Mild | Night-time behaviours occur but they are not particularly disruptive | <input type="checkbox"/> |
| 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 | <input type="checkbox"/> |
| 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 | <input type="checkbox"/> |

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour/ did you find this behaviour when it was at its worst?"

- | | | |
|----|---------------------------------|--------------------------|
| 0. | Not at all..... | <input type="checkbox"/> |
| 1. | Minimally..... | <input type="checkbox"/> |
| 2. | Mildly..... | <input type="checkbox"/> |
| 3. | Moderately..... | <input type="checkbox"/> |
| 4. | Severely..... | <input type="checkbox"/> |
| 5. | Very severely or extremely..... | <input type="checkbox"/> |

Caregiver distress score

L. Appetite and Eating Disorders

"Has he/she had any change in appetite, weight or eating habits (count as 'No applicable' if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?"

Yes No

If 'Yes' proceed to sub-questions,
If 'No' proceed to next screening question

		Yes	No
1.	Has he/she had a loss of appetite?	<input type="checkbox"/>	<input type="checkbox"/>
2.	Has he/she had an increase in appetite?	<input type="checkbox"/>	<input type="checkbox"/>
3.	Has he/she had a loss of weight?	<input type="checkbox"/>	<input type="checkbox"/>
4.	Has he/she gained weight?	<input type="checkbox"/>	<input type="checkbox"/>
5.	Has he/she had a change in eating behaviour such as putting too much food in his/her mouth at once?	<input type="checkbox"/>	<input type="checkbox"/>
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?	<input type="checkbox"/>	<input type="checkbox"/>
7.	Has he/she developed eating behaviours such as eating exactly the same types of food each day or eating the food in exactly the same order?	<input type="checkbox"/>	<input type="checkbox"/>
8.	Have there been any other changes in appetite or eating that I haven't asked about?	<input type="checkbox"/>	<input type="checkbox"/>

"When were these behaviours at their worst?"

In the last month / Now as bad as ever	<input type="checkbox"/>
1-6 months ago	<input type="checkbox"/>
6 months-1 year ago	<input type="checkbox"/>
1 year - 3 years ago	<input type="checkbox"/>
More than 3 years ago	<input type="checkbox"/>

"Do they still occur?"

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

"If no, when did they last occur?" (in months)

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

"Now I want to find out how often these things {define using the description of the behaviour} occur. When they were at their worst, would you say that they occurred less than once a week, about once a week, several times a week but not every day or every day?"

Frequency

- 1. Occasionally - less than once per week
- 2. Often - about once per week
- 3. Frequently - several times per week but less than every day
- 4. Very frequently - once or more per day

"Now I would like to find out how severe these things are. By severity I mean how disabling they are to the patient. When they were at their worst would you say they were mild moderate or severe?"

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 fluctuations in weight.
- 3. Marked Obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing or otherwise disturb the patient.

If applicable and rated, please enter the score (frequency x severity)

"How emotionally distressing do you find this behaviour / did you find this behaviour when it was at its worst?"

- 0. Not at all.....
- 1. Minimally.....
- 2. Mildly.....
- 3. Moderately.....
- 4. Severely.....
- 5. Very severely or extremely.....

Caregiver distress score

7.4 Additional Analysis

7.4.1 Data in Transformed Scale

Appendix Table 1: Mean and SE Values of Neuropsychological Tests in Transformed Scale

		T-Mean	T-SE	UT-Mean	UT-SE
MMSE	Non-Psychotic	3.48x10 ⁵ (24.28) ^b	170947	23.53	0.62
	Psychotic	2.68x10 ⁵ (22.75) ^b	202893	20.88	0.98
Delayed Visual Recall	Non-Psychotic	0.39 ^a (1.45) ^b	0.06	2.47	0.46
	Psychotic	0.31 ^a (1.04) ^b	0.06	1.50	0.30
Incomplete Letters	Non-Psychotic	335.83 ^a (18.33) ^b	15.36	18.39	0.24
	Psychotic	263.74 ^a (16.25) ^b	16.09	15.59	0.76

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education. T = Transformed (MMSE = x^4 , Delayed Visual Recall = $\text{Log}_{10}(x+1)$, Incomplete Letters = x^2) used in analysis. UT = Untransformed. ^bBack-Transformed mean.

7.4.2 Statistical Analysis After Removing 6 Subjects Not Experiencing Psychotic Symptoms at the Time of Assessment

Appendix Table 2: Motor Speed

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Simple Reaction Time (seconds)	Non-Psychotic	431.13 ^a	21.89	1.87	0.18	0.03
	Psychotic	481.04 ^a	25.58			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education. n = 27 in psychotic group as 1 subject was unable to complete this task.

Appendix Table 3: Sustained Attention

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Rapid Visual Processing (accurate responses out of 24)	Non-Psychotic	19.10 ^a	0.67	4.55	0.04*	0.08
	Psychotic	16.86 ^a	0.79			

Note: ^aAdjusted mean with constant covariates - transformed MMSE and years of education. n = 24 in psychotic group as four subjects were unable to complete the task, and n = 34 in non-psychotic group as two subjects were unable to complete this task. * Significant main effect at p<0.05.

Appendix Table 4: Executive Function

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Semantic Fluency (number of words)	Non-Psychotic	22.21 ^a	1.02	0.82	0.56	0.10
	Psychotic	20.70 ^a	1.35			
Phonemic Fluency (number of words)	Non-Psychotic	24.67 ^a	1.56			
	Psychotic	24.31 ^a	2.05			
Digit span (maximum = 30)	Non-Psychotic	13.28 ^a	0.42			
	Psychotic	12.62 ^a	0.55			
Hayling Inhibition time (seconds)	Non-Psychotic	127.43 ^a	10.64			
	Psychotic	104.92 ^a	14.02			
Hayling total errors (maximum = 15)	Non-Psychotic	9.76 ^a	0.65			
	Psychotic	10.62 ^a	0.86			
Go/No-Go Probability of Inhibition (%)	Non-Psychotic	79.17 ^a	2.07			
	Psychotic	78.03 ^a	2.73			

Note: ^aAdjusted mean with constant covariates - transformed MMSE and years of education. n = 20 in psychotic group as eight subjects were unable to complete at least one of the tasks from this cognitive domain, and n = 34 in non-psychotic group as two subjects were unable to complete at least one of the tasks.

Appendix Table 5: Memory

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Immediate Verbal Recall (maximum = 30)	Non-Psychotic	10.18 ^a	0.52	0.68	0.64	0.06
	Psychotic	10.77 ^a	0.60			
Delayed Verbal Recall (maximum = 10)	Non-Psychotic	1.04 ^a	0.23			
	Psychotic	1.49 ^a	0.27			
Delayed Visual Recall [†] (maximum = 14)	Non-Psychotic	0.38 ^a (1.39) ^b	0.06			
	Psychotic	0.33 ^a (1.13) ^b	0.07			
Delayed Verbal Recognition (maximum = 20)	Non-Psychotic	15.40 ^a	0.50			
	Psychotic	15.84 ^a	0.57			
Delayed Visual Recognition (maximum = 25)	Non-Psychotic	17.36 ^a	0.58			
	Psychotic	16.78 ^a	0.67			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education.

[†]Data transformed to fit homogeneity of variance assumption, mean and SE in transformed scale $\log_{10}(x+1)$. ^bBack-transformed mean.

Appendix Table 6: Language

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Boston Naming Test (maximum = 15)	Non-Psychotic	11.58 ^a	0.42	0.73	0.40	0.01
	Psychotic	11.01 ^a	0.48			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education.

Appendix Table 7: Constructional Praxis

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Total Praxis score (maximum = 11)	Non-Psychotic	9.04 ^a	0.33	1.24	0.30	0.04
	Psychotic	8.24 ^a	0.37			
Clock Drawing Task (scale 1-6, maximum = 1)	Non-Psychotic	3.23 ^a	0.21			
	Psychotic	3.39 ^a	0.24			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education. n = 35 in non-psychotic group as 1 subject from each group was unable to complete at least 1 of the tasks in this domain.

Appendix Table 8: Visuoperceptual Function

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Incomplete Letters ^t (maximum = 20)	Non-Psychotic	335.32 (18.31) ^b	13.48	3.65	0.01 [*]	0.21
	Psychotic	274.02 (16.55) ^b	15.73			
Object Decision (maximum = 20)	Non-Psychotic	15.33 ^a	0.50			
	Psychotic	13.70 ^a	0.59			
Number Location (maximum = 10)	Non-Psychotic	7.43 ^a	0.46			
	Psychotic	6.65 ^a	0.53			
Cube Analysis (maximum = 10)	Non-Psychotic	6.91 ^a	0.41			
	Psychotic	7.12 ^a	0.48			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education. n = 27 in psychotic group as one subject was unable to complete at least one of the tasks in this domain. ^{*}Significant main effect at p<0.025 as Levene's test was significant (p<0.001) for Incomplete Letters. ^tData transformed to fit normality assumption, mean and SE in transformed scale. ^bBack-transformed mean.

Appendix Table 9: Visuoperceptual Function - Posthoc Pairwise Comparisons

Test	F-ratio	P-Value	η_p^2
Incomplete Letters [†] (maximum = 20)	8.14	0.006*	0.12
Object Decision (maximum = 20)	4.16	0.046	0.07
Number Location (maximum = 10)	1.16	0.29	0.02
Cube Analysis (maximum = 10)	0.10	0.76	0.002

Note: [†]Data transformed to fit normality assumption. *Significant at Bonferroni adjusted alpha level, $p < 0.0125$.

7.4.3 ANCOVA to Assess Between-Group Differences in Motor Latency, as Measured by the Motor Screening Task From the CANTAB

Appendix Table 10: Motor Latency (MOT)

Test	Group	Mean	SE	F-ratio	P-value	η_p^2
Motor Screening Task (MOT) (seconds)	Non-Psychotic	1442.20 ^a	100.94	0.02	0.89	<0.001
	Psychotic	1463.54 ^a	104.07			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education.

7.4.4 ANCOVA to Assess Between-Group Differences in VOSP Screening Task: Subgroup Analysis

Appendix Table 11: VOSP Screening (out of 20)

Psychotic Subtype	Mean	SE	F-ratio	P-value	η_p^2
Non-Psychotic	19.37 ^a	0.19	2.70	0.053	0.11
Paranoid	18.72 ^a	0.30			
Misidentification	18.39 ^a	0.32			
Paranoid & Misidentification	18.87 ^a	0.40			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE and years of education.

7.4.5 ANCOVA to Assess Between-Group Differences on Incomplete Letters Task, with VOSP Screening Task as a Covariate

Appendix Table 12: Incomplete Letters Task

Psychotic Subtype	Mean	SE	F-ratio	P-value	η_p^2
Non-Psychotic	17.95 ^a	0.48	9.95	<0.001*	0.33
Paranoid	16.85 ^a	0.75			
Misidentification	13.20 ^a	0.81			
Paranoid & Misidentification	18.93 ^a	0.98			

Note: ^aAdjusted mean with constant covariates - age, transformed MMSE, years of education and VOSP Screening Task. *Significant main effect at $p < 0.025$ as Levene's test was significant ($p < 0.001$).

Appendix Table 13: Incomplete Letters Task – Pairwise Comparisons

Test	Psychotic Subtype		Mean difference (A-B)	SE	P-value
	A	B			
Incomplete Letters	Non-Psychotic	Paranoid	1.10	0.92	0.24
		Misidentification	4.75*	0.98	<0.001
		Paranoid & Misidentification	-0.98	1.12	0.39
	Paranoid	Misidentification	3.66*	1.11	0.002
		Paranoid & Misidentification	-2.08	1.24	0.10
	Misidentification	Paranoid & Misidentification	-5.73*	1.24	<0.001

Note: *Significant mean difference at $p < 0.05$. Multiple comparisons corrected for using Fisher's LSD.

7.4.6 Multicollinearity of variables in Logistic Regression Model

Appendix Table 14: Multicollinearity of Independent Variables

Independent variable	Age	Years of Education	MMSE	RVP	Incomplete Letters
Age		-0.06	-0.18	-0.14	-0.25
Years of Education			0.09	0.09	0.07
MMSE				0.49	0.36
RVP					0.37
Incomplete Letters					

Note: Spearman's rho presented as MMSE and Incomplete Letters violate assumptions for Pearson's correlation. Shaded cells represent values already presented within the table, or where the correlation is equal to 1.