Investigation in the overlap of ADHD and borderline personality disorder
A multi-modal approach

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Investigation in the overlap of ADHD and borderline personality disorder: A multi-modal approach

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Abstract

The nature of the relationship between attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) has been a subject of debate in recent years. The current thesis brings together a diversity of methodologies and approaches to investigate the similarities and differences of emotional dysregulation and mind wandering in ADHD and BPD.

Analyses in chapters 3, 4, and 5 are based on data from the PRIDE project, a case-control study of 114 adult females: 32 with ADHD, 19 with BPD, 27 with comorbid ADHD/BPD, and 36 psychiatrically healthy controls. Analyses in chapter 6 represent findings from a systematic review and meta-analysis investigating the effects of stimulants and atomoxetine on symptoms of emotional dysregulation in ADHD.

All the findings in this thesis point to the transdiagnostic nature of the overlapping symptoms of ADHD and BPD and of related impairments in various life domains, reflecting the heterogeneous picture of both conditions. The empirical findings of this thesis challenge the value of the categorical classification of ADHD and BPD, supporting instead a more dimensional and symptom-led approach of classification.

The research presented here has clinical implications for the identification and treatment of ADHD and BPD in adulthood.

Statement of work

Chapters 3, 4 and 5: The project idea, proposal and ethical approval for the Personality Research in ADHD and Emotional Instability (PRIDE) study was carried out in discussions between myself and my supervisors Professors Philip Asherson and Paul Moran. I was responsible for the recruitment, supervision and training of research staff working on the project, and was responsible for sourcing and preparing all the equipment and tasks used in this project. I carried out day-to-day project coordination over approximately three years and was the main contributor to recruitment, selection of participants, the organisation and carrying out of the assessments and the management of the data. All analyses presented in this thesis were carried out by me, under the supervision of Professors Asherson and Moran, and in chapters 4 and 5, they were additionally supervised by Professor Ulrich Ebner-Priemer and Dr. Iris Reinhard.

Chapter 6: The proposal for the meta-analysis was conceived by myself and my supervisors Professors Asherson and Moran. I carried out all aspects of the project: the literature search, quality assessment of studies (second rated by Professor Moran), data analysis, interpretation and write-up, whilst closely supervised by Dr. Evangelis Vassos and Dr. Ruth Cooper.

Publications relevant to this thesis

Chapter 1 includes sections adapted from the following review publication:

Moukhtarian, T.R., Mintah, R.S., Moran, P., Asherson, P. (2018). Emotion dysregulation in attention-deficit/hyperactivity disorder and borderline personality disorder. *Borderline Personality Disorder and Emotion Dysregulation*, *5*(1), 9.

Chapter 5 is the following manuscript under review:

Moukhtarian, T.R., et al. (Under Review). Wandering minds in Attention-Deficit/Hyperactivity Disorder and borderline personality disorder: An experience sampling investigation. *Journal of Abnormal Psychology*.

Chapter 6 is the following publication:

Moukhtarian, T.R., Cooper, R.E., Vassos, E., Moran, P., Asherson, P. (2017). Effects of stimulants and atomoxetine on emotional lability in adults: A systematic review and meta-analysis. *European Psychiatry*, *44*,198–207

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List of abbreviations

The following abbreviations will be referred to throughout this thesis and are redefined at first use in each new chapter.

ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS	ADHD- Rating Scale
AIC	Akaike Information Criteria
ALS-SF	Affective Lability Scale- Short Form
ANOVA	Analysis of Variance
ARI	Affective Reactivity Index
ATX	Atomoxetine
AUC	Area Under Curve
AUDIT-C	Alcohol Use Disorders Identification Test
BDI	Beck Depression Inventory
BIC	Bayesian Information Criterium
BLRT	Bootstrap Likelihood Ratio Test
BPD	Borderline Personality Disorder
BRIEF-A	Behaviour Rating Inventory of Executive Function - Adult Version
BSI	Brief Symptom Inventory
CAARS	Conner's Adult ADHD Rating Scale
CBT	Cognitive Behavioural Therapy
CI	Confidence Intervals
CM	Clinical Management
CTQ	Childhood Trauma Questionnaire
d	Cohen's D
DBT	Dialectical Behavioural Therapy
DIVA	Diagnostic Interview for ADHD In Adults
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EL	Emotional Lability
ES	Effect Size
ESM	Experience Sampling Method
fMRI	Functional Magnetic Resonance Imaging
GWAS	Genome Wide Association Studies
ICC	Intra-Class Correlation
ID	Identification
iFC	Intrinsic Functional Connectivity
IQ	Intelligence Quotient
ITT	Intent To Treat
LCA	Latent Class Analyses
MEWS	Mind Excessively Wandering Scale
MW	Mind Wandering
n	Number
NHS	National Health Service
OR	Odds Ratio
PRIDE	Personality Research in ADHD and Emotion Instability

List of abbreviations

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Post-Traumatic Stress Disorder
RCT	Randomised Controlled Trial
RDoC	Research Domain Criteria
ROC	Receiver Operating Characteristic
SAS	Statistical Analysis Software
SCID-II	Structured Clinical Interview for Axis-II
SCL	Symptom Check List
SGDP	Social, Genetic and Developmental Psychiatry
SMD	Standardised Mean Difference
SNP	Single Nucleotide Polymorphism
SPSS	Statistical Package for The Social Sciences
SSD	Squared Successive Difference
STATA	Software for Statistic and Data Science
SUC	Substance Use Checklist
WASI-II	The Weschler Abbreviated Scale of Intelligence II
WFIRS-S	Weiss Functional Impairment Rating Scale Self-Report
WRAADDS-EDS	Wender-Reimherr Adult Attention Deficit Disorder Scale- Emotional Dysregulation Subscale

Chapter 1: Introduction

1.1 Aim of this chapter

This thesis originates from clinically driven questions about the relationship between adult attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD). It aims to contribute to the understanding of the similarities and differences in the type of emotional dysregulation and mind wandering associated with both disorders. Ultimately the aim of this research is to inform future classification of these disorders. The general introduction is a synopsis of what is currently known about adult ADHD and BPD in general and more specifically about their clinical overlap. I present a detailed literature review relevant to the topics discussed in subsequent experimental chapters. Subsequently, I describe the overall aims and outline of this thesis.

1.2 Overview

In recent years, a debate has ensued over the nosological distinction between ADHD and BPD (Van Dijk, Lappenschaar, Kan, Verkes, & Buitelaar, 2012). Impulsivity, irritability and other symptoms of emotional dysregulation are characteristically seen in both disorders, but the nature of the relationship between ADHD and BPD requires clarification (Asherson et al., 2014). Key questions that arise include the extent to which: ADHD and BPD co-occur; they reflect distinct disorders or alternative expressions of the same underlying disorder; they share common genetic or environmental risk factors; or one of the disorders has a pathoplastic effect on the other (Storebø & Simonsen, 2014; Xenaki & Pehlivanidis, 2015). In this chapter I review the current literature regarding these key questions.

1.3 An introduction to attention-deficit/hyperactivity disorder

1.3.1 Historical context

ADHD is a common neurodevelopmental disorder, emerging in childhood or early adolescence, characterised by a pervasive pattern of developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity that lead to clinically significant functional and psychosocial impairments (American Psychiatric Association, 2013). The first reference of inattentive problems in children dates to

the late 18th century by the Scottish physician Alexander Chrichton and the German physician Melchior Adam Weikard (Barkley & Peters, 2012). From 1968, several diagnostic formulations for ADHD-like behaviours were incorporated in the Diagnostic and Statistical Manual for Mental Disorders (DSM). The first, 'hyperkinetic reaction of childhood', was accompanied by a shift in focus towards identifying and measuring behavioural features of the disorder (DSM-II; American Psychiatric Association, 1968). The second, heavily influenced by work on the central role of attention in the syndrome (Douglas, 1972), was labelled 'attention deficit disorder '(DSM-III; American Psychiatric Association, 1980). With emphasis returning to hyperactivity symptoms, ADHD was introduced in the DSM-III-revised (American Psychiatric Association, 1987). This diagnostic label continues to be used today, although instead of a unitary disorder, three ADHD presentations have been introduced (American Psychiatric Association, 2013). From the second revision of the DSM-II, diagnostic formulations no longer included emotional problems previously associated with minimal brain dysfunction (Barkley, 2011). From the DSM-III these were reassigned to 'associated features', where they remain today (American Psychiatric Association, 2013; Reimherr et al., 2005).

1.3.2 Diagnostic classification

There is no objective test for ADHD, and decisions to diagnose and treat ADHD are based on subjective (self and informant) reports assessed and interpreted by clinicians in light of diagnostic cut-offs (Okie, 2006).

According to the DSM–5, the diagnosis of ADHD requires six out of nine ADHD symptoms of either inattention or hyperactivity/impulsivity in childhood, and five out of nine symptoms in adults (American Psychiatric Association, 2013; see Table 1.1). Additional criteria include childhood age of onset, defined as several ADHD symptoms present before the age of 12 years, pervasiveness, defined as symptoms present in two or more settings, and impairment, defined as- interference with or reduced quality of social, academic or occupational functioning persistent for at least six months (Epstein & Loren, 2013).

Table 1.1 DSM-5 diagnostic criteria for ADHD

(A1) Inattention:
1 Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities
2 Often has difficulty sustaining attention in tasks or play activities
3 Often does not seem to listen when spoken to directly
4 Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure of comprehension)
5 Often has difficulty organising tasks and activities
6 Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
7 Often loses things necessary for tasks or activities at school or at home
8 Is often easily distracted by extraneous stimuli (may include unrelated thoughts)
9 Is often forgetful in daily activities
(A2) Hyperactivity:
10 Often fidgets with hands or feet or squirms in seat
11 Often leaves seat in classroom or in other situations in which remaining seated is expected
12 Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults may be limited to feeling restless)
13 Often has difficulty playing or engaging in leisure activities quietly
14 Often talks excessively
15 Is often "on the go" or often acts as if "driven by a motor"
Impulsivity:
16 Often has difficulty awaiting turn in games or group situations
17 Often blurts out answers to questions before they have been completed
18 Often interrupts or intrudes on others
Associated features supporting the diagnosis:
Emotional dysregulation (low frustration tolerance, emotional over-reactivity, or mood lability, as featured in the Wender-Utah adult ADHD criteria) [a]
Mild delays in language, motor, or social development
Impaired academic or work performance [a]
Increased risk of suicide attempts by early adulthood, primarily when comorbid with mood, conduct or substance use disorders [a]

[a] Behavioural symptom that commonly overlaps with BPD diagnosis

In addition to the main symptoms used to classify ADHD, emotional dysregulation is considered to be an associated feature supporting the diagnosis of ADHD (American Psychiatric Association, 2013; Asherson, Buitelaar, Faraone, & Rohde, 2016). In ADHD, emotional dysregulation is characterised by problems with temper control (feelings of irritability and frequent outbursts of short duration), emotional over-reactivity (diminished ability to handle typical life stresses, resulting in frequent feelings of being hassled and overwhelmed), and mood lability (short and unpredictable shifts from normal mood to depression or mild excitement) (Reimherr et al., 2005).

Excessive mind wandering is thought to reflect a measurable component of ADHD psychopathology, potentially distinguishing it from other psychiatric conditions (Mowlem et al., 2016). Mind wandering is a universal phenomenon that takes up around 50% of daily thinking time (Smallwood & Schooler, 2015) and occurs when one's mind drifts away from the primary task at-hand and instead focuses on internal, task-unrelated thoughts and images (Smallwood, McSpadden, & Schooler, 2007). Although not all forms of mind wandering reflect pathological processes (Seli, Smallwood, Cheyne, & Smilek, 2015), excessive spontaneous mind wandering, that is detrimental to performance, has been proposed as a possible mechanism underlying many of the impairments of ADHD (Bozhilova, Michelini, Kuntsi, & Asherson, 2018; Mowlem et al., 2016).

1.3.3 Prevalence and gender differences

ADHD is considered one of the most highly prevalent childhood psychiatric disorders, affecting around 5% of children (Polanczyk, De Lima, Lessa Horta, Biederman, & Rohde, 2007). Longitudinal follow-up studies of children with ADHD show that symptoms of ADHD commonly persist into adulthood, with around two-thirds of cases meeting either full or sub-threshold criteria in adulthood (Brookes et al., 2006). The prevalence of adult ADHD in epidemiological surveys is estimated at around 2.5-4% in the general population (De Graaf et al., 2008; Fayyad et al., 2007; Kessler et al., 2006). Although there is the possibility that ADHD might emerge after childhood (Moffitt et al., 2015), for most adult patients with ADHD there is a clear history of ADHD from childhood. The lower prevalence of ADHD in adulthood may be explained by reductions in ADHD symptoms and impairment throughout development in a subset of people with ADHD, difficulties in self-recognition of ADHD symptoms, and potentially altered expression of ADHD symptoms, such as hyperactivity being manifested as feelings of restlessness (Asherson et al., 2014).

ADHD is recognised as a predominantly male disorder in childhood, with male to female ratios generally ranging from 3:1 in population-based studies, to 9:1 in clinic-referred studies (Ford, Goodman, & Meltzer, 2003; Polanczyk et al., 2007). However, in adult clinical samples and epidemiological studies on adult ADHD,

the sex difference is less pronounced (Bernardi et al., 2012; Kessler et al., 2006; Rucklidge, 2010). In a meta-analysis of epidemiological studies of ADHD in adults, Simon and colleagues (2009) identified an age-by-sex interaction, with younger adults with ADHD being characterised by a much larger male preponderance.

1.3.4 Associated impairments and comorbidity

The symptom profile and severity of ADHD varies greatly between individuals, with both inattention and hyperactivity/impulsivity associated with functional impairment in multiple domains (Asherson, Chen, Craddock, & Taylor, 2007; Asherson et al., 2014). Emotional dysregulation has also been found to be an independent predictor of impairment in ADHD, after controlling for the confounding effects of core ADHD symptoms (inattention and hyperactivity/impulsivity) on impairment (Asherson et al., 2015; Barkley & Fischer, 2010; Skirrow & Asherson, 2013). Furthermore, emotional dysregulation has been found in cases of ADHD with no co-existing mental health disorders, and therefore cannot always be explained by co-occurring conditions (Skirrow et al., 2014). Impairments can be severe, impacting on education, occupation, social and interpersonal relationships (Asherson et al., 2007; Asherson et al., 2014). Adults with ADHD are more likely to have lower educational attainment, poorer work performance and an increased likelihood of dismissal from work (Gjervan, Torgersen, Nordahl, & Rasmussen, 2012; Halmøy, Fasmer, Gillberg, & Haavik, 2009; Rösler, Casas, Konofal, & Buitelaar, 2010), as well as difficulties in maintaining long-term social relationships and higher divorce rates (Barkley & Murphy, 2010), serious transport accidents (Chang, Lichtenstein, D'Onofrio, Sjolander, & Larsson, 2014), and criminality (Lichtenstein & Larsson, 2013).

High comorbidity rates are a widespread phenomenon in psychiatric research, even in non-referred community samples (Kessler et al., 2005; Weich et al., 2011). ADHD seldom exists in isolation and up to 90% of adults with ADHD in clinical and population samples are reported to have one or more co-occurring mental health disorders (Bolea-Alamanac et al., 2007). Of these disorders, the most prevalent include depressive disorders (35-50%), anxiety disorders (40-60%), substance use disorders (up to 50%) (Cumyn, French, & Hechtman, 2009;

Sobanski, 2006; Xenaki & Pehlivanidis, 2015), and personality disorders including BPD (Davids & Gastpar, 2005; van Dijk, Lappenschaar, Kan, Verkes, & Buitelaar, 2011). This exceptionally high co-morbidity rate could however reflect, at least in part, an artefact of overlapping symptoms shared by other mental health disorders (Asherson et al., 2016). It could also reflect measurement error, resulting from a reliance on self-reported rating scales. Irrespective of the underlying cause of co-morbidity, several lines of research have investigated the extent to which the shared aetiological factors may explain the co-occurrences of these psychiatric conditions with ADHD. For example, twin studies suggest moderately large shared genetic effects (genetic correlation; r_A=.50-.77) for the co-occurrence of ADHD with depression and anxiety (Cole, Ball, Martin, Scourfield, & McGuffin, 2009; Michelini, Eley, Gregory, & McAdams, 2015), and this is supported from findings from the latest genome wide association studies (GWAS) using linkage disequilibrium regression analysis (Demontis et al., 2017).

Despite the high prevalence of adult ADHD and established links to psychosocial and functional impairments, as well as its co-occurrence with other psychiatric disorders, high rates of undiagnosed or untreated ADHD have been found in clinical settings (Huntley et al., 2012). Additionally, understanding the similarities and differences between adult ADHD and common co-occurring mental health disorders is important to improve understanding of the clinical presentation of ADHD in adulthood, reduce under-diagnosis, and provide targeted and effective treatments. Further research is needed using neurobiological, genetic and environmental measures to better understand the common aetiological mechanisms which explain their co-occurrence with ADHD.

1.3.5 Aetiology of ADHD

ADHD is a complex disorder with a multifactorial aetiology, which arises from the interplay between genetic and environmental risk factors (Faraone et al., 2015). During the past decade, quantitative genetic research has established that ADHD runs in families and is largely influenced by genetic factors, while individual-specific environmental factors may also play a limited role. These findings have led to efforts to explore and identify the specific genetic variants that underlie the

ADHD phenotype. There have also been efforts in identifying environmental risk factors in ADHD and studying how they interact with genes. These research efforts have highlighted the complexity of aetiological pathways to ADHD and how much is still to be learned. Further details of the genetic and environmental risks involved, are outlined in section 1.5.5.

1.4 An introduction to borderline personality disorder

1.4.1 Historical context

In the early 1900s, a subset of patients presenting with a pattern of symptoms and behaviours that were inconsistent with any predefined diagnostic category and considered to lie at the border between neurosis and psychosis, were labelled "borderline" (Stern, 1938). These patients who appeared depressed and anxious also exhibited temporary psychotic symptoms in stressful situations. The first systematic attempt to describe a borderline patient was undertaken by the psychoanalyst Adolph Stern in 1938. In the following years, the term "borderline" developed from being considered a personality organisation, to a syndrome, then to a disorder, with the term BPD first being introduced in the DSM-III (American Psychiatric Association, 1980). Since its introduction in the DSM, BPD has undergone relatively minor changes to the diagnostic criteria.

1.4.2 Diagnostic classification

BPD is a complex and severe mental health disorder, with typical symptom onset during adolescence and presence of behavioural precursors in childhood, persisting into adulthood (American Psychiatric Association, 2013). BPD is characterised by a pervasive pattern of unstable interpersonal relationships, pronounced impulsive and self-damaging behaviour, unstable identity, and difficulties with emotional dysregulation (American Psychiatric Association, 2013), which substantially impact in an enduring way on quality of life and psychosocial functioning (Gunderson, Stout, et al., 2011). The DSM-5 diagnosis of BPD requires the pervasive presence of a minimum of five out of nine symptoms for at least one year, present in a variety of contexts (American Psychiatric Association, 2013; see Table 1.2).

Table 1.2 DSM-5 symptom criteria for borderline personality disorder

1 Frantic efforts to avoid real or imagined abandonment
2 A pattern of unstable[a] and intense interpersonal relationships
3 Impulsivity in at least two areas that are potentially self-damaging[a]
4 Identity disturbance: markedly and persistently unstable self-image or sense of self
5 Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour
6 Affective instability due to a marked reactivity of mood[a]
7 Chronic feelings of emptiness
8 Inappropriate, intense anger or difficulty controlling anger[a]
9 Transient, stress-related paranoid ideation or severe dissociative symptoms
Associated features supporting the diagnosis
Recurrent job losses, interrupted education, and separation or divorce are common[a]

[a]Behavioural symptoms that commonly overlaps with ADHD diagnosis

Problems with diagnosis and heterogeneity

The DSM personality disorders criteria, especially for BPD, are of a polythetic nature, inevitably resulting in a heterogenous group of patients. There are 126 different ways to meet the DSM criteria for BPD, and two borderline patients may share only one common symptom. This threatens the internal consistency of the BPD construct, challenging its validity as a single diagnostic entity (Trull & Durrett, 2005). Additionally, people often meet the criteria for more than one personality disorder. For example, approximately 25% of people diagnosed with BPD also meet the criteria for antisocial personality disorder (Zanarini et al., 1998).

1.4.3 Prevalence and gender differences

In the general population, based on cross-sectional and community-based surveys, BPD has a prevalence in the range of 1.4% to 6% (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006; Grant et al., 2008; Lenzenweger, Lane, Loranger, & Kessler, 2007). Within populations of adult psychiatric outpatients and patients in primary care, prevalence is around 20% (American Psychiatric Association, 2013; Grant et al., 2008). The disparity between prevalence figures may be due to variations in sampling, study setting and case ascertainment, with higher prevalence marked in urban areas (Tyrer, Reed, & Crawford, 2015).

Most epidemiological surveys report no sex differences for BPD, yet studies of clinical populations typically report much higher prevalence in women, than in men

(Zimmerman, Rothschild, & Chelminski, 2005). Approximately 75% of BPD diagnoses are in females (American Psychiatric Association, 2013). The difference in prevalence may reflect real sex differences, although the finding that there is no prevalence difference in epidemiological surveys may well reflect variation in methodology (population, sampling, case detector) used (Grant et al., 2008). Additionally, childhood trauma, notably sexual abuse, is more frequently reported in females than males, 70% versus 50% based on epidemiological studies (Jonas et al., 2010; Skodol & Bender, 2003). Given the strong association of BPD with sexual abuse, this may partly explain the higher incidence in treatment seeking females. The sex variations may also reflect a real difference in the biology, with affective instability in males more often resulting in externalising behaviour in the form of aggression (which may translate to antisocial personality disorder in extreme cases), and in women, this more often manifests as internalising pathology in the form of depression and self-harm (Paris, 2004). Males may also be less likely to seek out psychological help or more likely to end up in the criminal justice system (Bateman & Krawitz, 2013; Tyrer et al., 2015). Sansone and Sansone (2011) noted that research studies traditionally sample inpatient psychiatric patients to determine prevalence of BPD, which would result in an underestimate of the number of men with BPD.

1.4.4 Comorbidities and associated impairments

Like ADHD, individuals with BPD commonly present with comorbid mental health disorders. In particular, around 90% of BPD cases are reported to have co-occurring mood disorders, including depression and dysthymia (Zanarini et al., 1998), anxiety, post-traumatic stress disorder, and a high prevalence of substance use disorders in the range of 15% to 57% (Sharp & Romero, 2007). This high comorbidity could potentially result in some individuals with BPD remaining undiagnosed, placing them at risk for ineffective or even harmful treatment (Tyrer et al., 2015).

The potential consequences of BPD for future health and social functioning are stark. Studies suggest that approximately 10% of individuals with BPD die prematurely by committing suicide (Paris, 2002). Individuals with any personality

disorder are also more likely to be separated or divorced, and unemployed or economically inactive (Coid et al., 2006). Those with BPD, however, are especially likely to demonstrate significant impairment at work, in social relationships and leisure pursuits (Skodol et al., 2002). Family life is often affected, and less than half of BPD patients get married, with even fewer having children (Paris, 2003). Overall, the evidence suggests that individuals suffering from BPD have a severely reduced quality of life and sustained functional impairment (Zanarini, Frankenburg, Hennen, Reich, & Silk, 2005).

1.4.5 Aetiology of BPD

The aetiology of BPD is not fully understood and given the heterogenous nature of the disorder, a bio-psychosocial model is likely to be the most informative to understand it. Nevertheless, some neurobiological and genetic explanations have also been put forth. Neuroimaging studies have shown possible structural differences in brain regions of people with BPD, in comparison with matched controls (Krause-Utz, Winter, Niedtfeld, & Schmahl, 2014); dysfunctions in the prefrontal cortex as a source for attentional mechanisms, and altered activation of the orbitofrontal cortex as a core region for impulsivity and emotional instability (Krause-Utz et al., 2014, Philipsen, 2006). Like ADHD and other complex behavioural disorders, single gene effects have not been identified as causative of BPD (Chanen & McCutcheon, 2013), and genetic risks are expected to arise from multiple genes of small effect (Amad, Ramoz, Thomas, Jardri, & Gorwood, 2014). Genetic vulnerability may begin to explain the development of BPD but must be considered alongside developmental processes and the impact of exposure to environmental risks.

Adverse childhood experiences play a key role in the development of BPD and include childhood maltreatment (Cohen et al., 2013), and exposure to parental psychopathology (Zanarini & Frankenburg, 1997). These experiences appear to lead to attachment disturbances (Fonagy, Target, Gergely, Allen, & Bateman, 2003). Difficulties in development of cognitions (Beck et al., 2001), emotions (Carpenter & Trull, 2013), behaviours and interpersonal relationships have also been highlighted in BPD. Of note, these processes cannot be considered as

exclusive to any one mental health disorder, and this might explain the higher rates of comorbidity. Overall, it is likely that a number of different causal factors, environmental as well as individual differences in genetics and biology, and processes are involved, as individuals with the same risk factors do not all develop BPD (Cicchetti, 2014). Further details of the genetic and environmental risks are outlined in section 1.5.5.

1.5 Overlap in ADHD and BPD

1.5.1 Studies of the co-morbidity between ADHD and BPD

Psychiatric comorbidity is commonly found across all mental health disorders (Kessler et al., 2005) and is defined as the presence of two or more disorders in the same individual at a given time. In principle, each of the disorders should make a unique contribution to the clinical presentation of the individual (Vella, Aragona, & Alliani, 2000). However, estimates of comorbidity prevalence may be inflated if there is marked overlap in the symptom criteria of two disorders, leading to poor diagnostic delineation i.e. artefactual co-morbidity (Skirrow, Hosang, Farmer, & Asherson, 2012). Furthermore, it remains unclear to what extent psychiatric diagnoses reflect entirely distinct disorders, rather than overlapping syndromes (Vella et al., 2000). This is a particular problem for psychiatry, because as yet, there are no validated biomarkers or other objective markers with sufficient sensitivity or specificity to be used in clinical practice to distinguish aetiologically distinct mental health conditions. Regarding ADHD and BPD, while the specific symptoms used to classify the two disorders are different, many clinical characteristics are shared, including emotional dysregulation, impulsive risk-taking behaviour, and unstable interpersonal relationships.

A high prevalence of co-occurring ADHD and BPD is consistently reported in the literature. In a large in- and outpatient cohort of 372 adults with ADHD referred for ADHD assessment and treatment at a tertiary referral centre, 27.2% also met criteria for BPD assessed by the Structured Clinical Interview for DSM-IV Axis II (SCID-II) (Jacob et al., 2007). Similarly, in another sample of 335 adults referred by family physicians, community health clinics or self-referred, BPD, assessed by the SCID-II, was reportedly present in 10% of patients with DSM-IV inattentive

subtype ADHD (six or more symptoms of inattention) and 24% of patients with combined subtype ADHD (six or more symptoms of both inattention and hyperactivity/impulsivity) (Cumyn et al., 2009). Likewise, in a sample of 181 adult patients diagnosed with BPD by general practitioners and referred for treatment, 38.1% had comorbid ADHD, with 22.7% meeting the combined type criteria (Ferrer et al., 2010).

In a sample of 118 adult women from out-patient clinics seeking treatment for BPD, a high co-occurrence rate was reported: 41.5% met criteria for childhood ADHD (assessed retrospectively), and 16.1% met current criteria for the DSM-IV combined subtype, as well as meeting ADHD criteria as children (Philipsen et al., 2008). However, as opposed to the previous studies where diagnoses were confirmed by clinical interviews (Cumyn et al., 2009; Ferrer et al., 2010; Jacob et al., 2007), severity of borderline personality disorder and ADHD symptoms were assessed using self-report questionnaires (Philipsen et al., 2008).

In a sample of adolescents (n=107) with emerging BPD drawn from a European research project investigating the phenomenology of BPD in adolescence, the prevalence of ADHD was 11%, an estimate that was not attenuated even when excluding symptoms of impulsivity accounting for possible symptom overlap (Speranza et al., 2011). This rate was close to the 16% rate found by Philipsen and colleagues, where current ADHD symptoms were assessed by self-report measures (Philipsen et al., 2008), as opposed to clinician-based interviews. Moreover, the samples significantly differed in regard to participants' age.

Regarding population samples, results from the National Epidemiologic Survey on Alcohol and Related Conditions of more than 34,000 adults, found that lifetime comorbidity with BPD in the ADHD population was 33.7% compared with a lower prevalence of BPD of only 5.2% in the general population (Bernardi et al., 2012).

1.5.2 Symptomatic overlap

There is considerable overlap in the symptoms of BPD and the associated features of ADHD (see Table 1.3). Considering the onset and developmental trajectory, both disorders can be considered 'developmental' in the sense that they both emerge

during childhood or adolescence and reflect enduring trait-like (non-episodic) symptoms and behaviours (Winsper et al., 2016). The shared general features of trait-like symptoms that characterise both ADHD and BPD; means that differentiating between these diagnoses cannot easily be established by considering age of onset and course of symptoms. This means that to a large extent, differential diagnosis is based on the specific symptoms and behaviours used to define the two disorders.

1.5.2.1 Impulsivity

The most noticeable overlap among the core symptoms used to classify both conditions is impulsivity (Speranza et al., 2011; Van Dijk et al., 2012). Nevertheless, there are important qualitative differences in the manifestation of impulsivity used in the classification of ADHD and BPD. In ADHD, impulsivity refers to difficulty waiting or taking turn, blurting out during conversations (e.g. interrupting or talking over people), and intruding on others (e.g. butting into conversations or activities, taking over what others are doing) (American Psychiatric Association, 2013). These impulsive symptoms are not always severe in adults with ADHD, but when severe, can lead to impairment in social functioning and self-damaging or risk-taking behaviour. The consequences of severe impulsivity in ADHD include reckless driving, promiscuity, interpersonal relationship problems and aggressive behaviour (McNamara, Vervaeke, & Willoughby, 2008; McNamara & Willoughby, 2010). In BPD, impulsivity is defined by self-damaging behaviour, such as reckless driving, shoplifting, spending, binge eating, substance abuse and promiscuity (American Psychiatric Association, 2013). People with either of these disorders may therefore display impulsive risk-taking behaviour, but from a diagnostic perspective, this is a core symptom of the BPD diagnosis, but only an associated feature of ADHD.

1.5.2.2 Emotional dysregulation

The other key area of symptom overlap is emotional dysregulation. Emotional dysregulation reflects a core symptom domain in the diagnostic classification of BPD (American Psychiatric Association 2013), whereas in ADHD it is recognised as an associated clinical feature that supports the diagnosis (Wender, 1995; Wood,

Reimherr, Wender, & Johnson, 1976). Nevertheless, emotional dysregulation is commonly seen to accompany ADHD, even in non-comorbid cases (Skirrow et al., 2012), and is an independent source of psychosocial impairment. This draws strong comparisons with emotional dysregulation in BPD, particularly when the emotional dysregulation that accompanies ADHD is severe (Berger, Kofman, Livneh, & Henik, 2007). At a descriptive level, the emotional symptoms of ADHD were well captured by Wender, Reimherr and colleagues in the earlier Wender-Utah criteria for ADHD and show substantial overlap with the emotional dysregulation symptoms in the DSM-5 BPD criteria (Philipsen et al., 2008; Xenaki & Pehlivanidis, 2015).

Emotional dysregulation is a dimensional construct (Shaw, Stringaris, Nigg, & Leibenluft, 2014), referring to rapid and exaggerated changes in emotional states such as heightened irritability or hot temper (Berger et al., 2007). A review by Asherson and colleagues reported that emotional dysregulation is present in 72-90% of adults with ADHD, and independently of other symptoms of ADHD predicts impairments in social, educational and occupational domains (Asherson, Kuntsi, & Taylor, 2005). In contrast, emotional dysregulation is one of the core symptom domains of individuals with BPD, who nearly always suffer from severe persistent affective instability, inner tension and difficulty controlling emotions such as anger (Davids & Gastpar, 2005; Philipsen, 2006; Philipsen et al., 2008, 2009). It has been suggested that patients with BPD have higher frequency and intensity of affective instability and aggressive impulsive reactions, compared to adults with ADHD (Ebner-Priemer, Welch, et al., 2007; Philipsen et al., 2009; Van Dijk et al., 2012). Others describe ADHD patients as being high novelty seekers, who regulate their emotions through extreme external stimulation (e.g. sexual activity, aggressive behaviour), as opposed to those with BPD, who tend to engage in self-mutilating behaviour to alleviate negative affect and inner tension (Philipsen, 2006). However, self-harming behaviour and suicidality in ADHD has been highlighted in recent literature (Allely, 2014). Yet, phenomenologically, emotional dysregulation is a complex construct, with shared characteristics in both ADHD and BPD, particularly pertaining to feelings of heightened anger and difficulty controlling anger (criterion eight in BPD) (Philipsen et al., 2008). Others suggest that emotional dysregulation reflects an underlying cyclothymic temperament present in both

disorders (Eich et al., 2014). Arguments in favour of considering emotional dysregulation as a core component of ADHD include the evidence that ADHD medication has a similar effect size (ES) on reducing emotional dysregulation as the core ADHD symptoms of inattention and hyperactivity/impulsivity (Reimherr, Marchant, Gift, Steans, & Wender, 2015; Rosler et al., 2010). On the other hand, emotional dysregulation is a domain that is seen to occur across a wide range of other psychiatric and neurodevelopmental disorders (American Psychiatric Association, 2013).

Regarding the overlap between ADHD and BPD, it remains unclear whether the type of emotional dysregulation seen in ADHD is qualitatively similar or different from that seen in BPD. One way to investigate this issue with precision is by using ambulatory assessments.

Table 1.3 Overlapping features between ADHD and BPD

ADHD	BPD
• Childhood or early adolescent onset (note: recent literature highlights early adult onset in some cases) (Moffitt et al., 2015)	• Adolescent or early adult onset
• Chronic (trait-like) symptoms and persistent course	• Chronic (trait-like) symptoms and persistence course
• Pattern of unstable interpersonal relationships is a common associated characteristic	• Pattern of unstable interpersonal relationships
• Affective instability is common associated characteristic	• Affective instability
• Risk taking behaviour (behavioural impulsivity) is an associated characteristic	• Behavioural impulsivity/risk taking
• Inappropriate anger or difficulty controlling anger is a common associated characteristic	• Inappropriate anger or difficulty controlling anger

1.5.3 Emotional dysregulation in ambulatory assessments

Emotions are time- and context-dependent processes which are not adequately captured by retrospective and cross-sectional reports (Ebner-Priemer & Trull, 2009). Yet, within clinical environments, assessment of emotional dysregulation relies entirely on interviews and self-report rating scales, which may be highly subjective and based on retrospective recall. These methods limit the validity of assessments of fluctuating emotional symptoms by the reliance on the individual's memory and the skills of the interviewer. They may also be coloured by the subject's mental state at the time of the assessment (Ebner-Priemer & Trull, 2009; Trull & Ebner-Priemer,

2014). For instance, it has been reported that BPD patients fail to remember their most extreme and intense mood changes (Santangelo, Bohus, & Ebner-Priemer, 2012). One alternative approach with greater ecological validity is to use repeated ratings of real-time experiences (Santangelo et al., 2014) - an approach which is termed ecological momentary assessments, ambulatory assessment or experience sampling method (ESM). ESM provides an effective way of precisely measuring emotional dynamics and variation within individuals, over time (Myin-Germeys et al., 2009; Skirrow et al., 2014).

In BPD, eight ESM studies have investigated the dynamics of emotional instability (Ebner-Priemer et al., 2015; Ebner-Priemer, Kuo, et al., 2007; Ebner-Priemer & Sawitzki, 2007; Ebner-Priemer & Trull, 2009; Ebner-Priemer, Welch, et al., 2007; Santangelo et al. 2014). In one study of 50 BPD and 50 healthy controls using 24-hour ambulatory monitoring (intervals of 15 minutes), the BPD group was found to overestimate emotions with negative valence and underestimate emotions with positive valence, when comparing retrospective with ESM ratings (Ebner-Priemer, Kuo, et al., 2007; Ebner-Priemer et al., 2006). In contrast, the healthy control sample overestimated emotions with positive valence and underestimated emotions with negative valence (Ebner-Priemer, Kuo, et al., 2007; Ebner-Priemer et al., 2006). Individuals with BPD have also been found to report greater levels of intra-individual variability and short-term fluctuations in overall affect valence. In another study comparing 34 outpatients with BPD and 26 with current depression, using ESM for nearly one month, ratings indicated greater instability (i.e. more changes from one assessment to the next) over time for fear, hostility and sadness in the BPD group (Trull et al., 2008). It has also been reported using ESM that compared to healthy controls, BPD patients experience a higher frequency and increased intensity of negative affect and a lower frequency and decreased intensity of positive affect (Ebner-Priemer, Kuo, et al., 2007; Ebner-Priemer & Sawitzki, 2007; Ebner-Priemer & Trull, 2009; Ebner-Priemer, Welch, et al., 2007). In addition, a recent review of 34 ESM studies found that BPD patients experience longer durations of aversive tension and therefore a slower return to their baseline affective state (Santangelo et al., 2012).

To our knowledge, there has been only one ESM study looking at the variation in emotional instability in adults with ADHD (Skirrow et al., 2014). Compared to healthy controls (n=47), patients with ADHD (n=41) showed significantly increased instability and intensity of negative emotions (irritability, frustration and anger). They also showed greater reactivity of negative emotions, such as anger, to 'bad' life events. This study included only males and specifically excluded patients with comorbid conditions (Skirrow et al., 2014).

Critically, from the standpoint of contrasting emotional dysregulation in populations of patients with ADHD and BPD, there have been no studies of the phenomenon in both patient groups using ESM. Furthermore, additional information could also be collected regarding the naturalistic context and situation when emotional changes occur (e.g. where they are, who they are with, what has just happened); which might identify disorder specific contextual triggers for emotional changes in different disorders. Clearly this area needs more research before conclusions can be drawn about the similarity or differences of emotional dysregulation in BPD and ADHD.

1.5.4 Neurobiological correlates of emotional dysregulation in ADHD and BPD

The overlap in symptoms of emotional dysregulation in ADHD and BPD raises the question of a common neurobiological substrate for emotional dysregulation in the two conditions. In ADHD, two competing hypotheses have been proposed for emotional dysregulation. First, the 'dyscontrol hypothesis' proposes that emotional dysregulation is driven by the same cognitive and neural processes that drive ADHD; for example, deficits in top-down executive control (from the prefrontal cortex to the amygdala), or bottom-up state regulation factors (from the limbic system to higher cortical regions) (Posner, Kass, & Hulvershorn, 2014; Thompson, 2011). In this model, emotional dysregulation reflects an alternative expression of the same underlying neurocognitive deficits that lead to ADHD symptoms. The alternative 'affectivity hypothesis' states that emotional dysregulation reflects deficits in neural processes related directly to emotional regulation, separate from those that lead to ADHD symptoms (Posner et al., 2014). To date the accumulating

evidence is pointing to the affectivity hypothesis. Two key publications support this conclusion (Banaschewski et al., 2012; Hulvershorn et al., 2014). First, a large multi-site investigation of cognitive performance deficits in 424 carefully diagnosed ADHD cases and their 564 unaffected siblings (including inhibition, working memory, impulsive responding, slow and variable reaction times), found these were associated with ADHD symptoms independently from emotional dysregulation (Banaschewski et al., 2012). This suggests that different processes would explain the presence of emotional dysregulation in ADHD. Subsequently, a resting state functional Magnetic Resonance Imaging (fMRI) study in children with ADHD, found that emotional dysregulation, independently from ADHD, was associated with increased positive intrinsic functional connectivity (iFC) between bilateral amygdala and medial prefrontal regions, and reduced iFC between amygdala and bilateral insula/superior temporal gyrus. These findings suggested that emotional dysregulation is linked to specific disruptions in emotional control networks, more specifically in the amygdala networks, that underlie emotion regulation impairments not linked directly to core ADHD symptoms (Hulvershorn et al., 2014).

Regarding ADHD, several different processes have been implicated, reflecting the potential heterogeneity of causal processes underpinning the development of ADHD symptoms (Faraone et al., 2015). These include: (1) reduced connectivity in the ventral fronto-striato-parietal (cognitive control) circuit; (2) reduced connectivity in the dorsal fronto-striato-parietal attention circuit; (3) reduced connectivity in inferior fronto-supplementary–motor-area-parieto-cerebellar networks for timing function; (4) reduced connectivity in orbitofrontal-ventral striatal (salience/reward) circuit; (5) reduced connectivity between the default mode network (DMN) and cognitive control circuits, linked to reduced deactivation of the DMN during cognitive tasks and reduced connectivity between components of the DMN (Cortese et al., 2012; Faraone et al., 2015).

Regarding BPD there are overlapping findings implicating the central role of emotional control networks. A critical review of fMRI studies concludes that emotional sensitivity, including emotional hypersensitivity and intense emotional reactions, was associated with increased amygdala activity and decreased activity

with prefrontal cortical control regions (van Zutphen, Siep, Jacob, Goebel, & Arntz, 2015). In particular, a consistent decrease in anterior cingulate activity and anterior insula was identified, while the medial and dorsolateral prefrontal areas showed variable activity across studies. Overall, increased limbic and diminished prefrontal cortical activity suggested an impaired fronto-limbic inhibitory network (van Zutphen et al., 2015).

A multi-centre study of resting-state fMRI, before and after an emotion regulation task in 48 patients with BPD from mental health clinics and 39 non-patients from the general population, further supports disrupted regulation of emotional circuits (Baczkowski et al., 2017). Emotional hypersensitivity in BPD was associated with increased intrinsic connectivity between the amygdala and bilateral insula together with dorsal anterior cingulate cortex, while their impaired control over emotional reactions was associated with diminished intrinsic connectivity between the central executive fronto-parietal regions and salience network (Baczkowski et al., 2017).

Overall, the pattern of findings in relation to emotion regulation was similar to that reported for emotional dysregulation in patients with ADHD by Hulvershorn et al. (2014). The overlap of these findings in relation to emotional dysregulation in the two disorders suggests that there may be a common substrate for emotional dysregulation in the two conditions, involving altered top-down and bottom-up regulation of amygdala function and neural circuits. However, as discussed *below*, evidence-based treatments are entirely different for the two disorders, suggesting that the underlying cause of the disrupted emotional circuits may differ in ADHD and BPD, potentially explaining differences in response to different treatments. Nevertheless, these findings suggest that there could also be common forms of treatment in at least a subset of patients with a comparable neurobiological basis for emotional dysregulation.

1.5.5 Genetic and environmental risk factors

1.5.5.1 Attention-deficit/hyperactivity disorder

It is firmly established that genetic factors play a central role in the aetiology of ADHD. The disorder aggregates among biological relatives of ADHD probands

(Epstein et al., 2000; Sprich, Biederman, Crawford, Mundy, & Faraone, 2000), and twin studies estimate heritability in the range of 70-80% for parent and teacher ratings of ADHD symptoms in children, with similar estimates for clinically diagnosed cases of ADHD (Epstein et al., 2000; Sprich et al., 2000). In adults, self-rating of ADHD symptoms lead to lower heritability estimates in the range of 30-50% (Brikell, Kuja-Halkola, & Larsson, 2015). However, heritability estimates are similar to those seen in children for the clinical diagnosis of ADHD, in adults, or when combining parent ratings and self-reports (Brikell et al., 2015; Chang, Zheng, Lichtenstein, Asherson, & Larsson, 2013; Larsson, Chang, D'Onofrio, & Lichtenstein, 2014). These studies find that the variance in ADHD in both childhood and adulthood is best explained by genetic and non-shared environmental factors, with no role for shared environmental factors independent of genetic influences (Brikell et al., 2015).

Earlier candidate gene studies found significant associations with genetic variation within dopamine and serotonin system genes (Gizer, Ficks, & Waldman, 2009), although the specific genes implicated in these earlier studies have not been identified in a more recent GWAS. Until recently, GWAS had not identified specific genetic variants that increase the risk of ADHD, although heritability due to the measured genetic variance was estimated to be around 30% (Middeldorp et al., 2016; Neale et al., 2010). The most recent GWAS, using a much larger sample of 20,183 ADHD cases and 35,191 controls identified twelve independent loci above genome-wide levels of significance ($p< 5x10^{-8}$), confirming the existence of numerous common variants of small effect that influence the development ADHD (Demontis et al., 2017). As these are recent findings, further research examining the role of these variants is required.

1.5.5.2 Borderline personality disorder

Though not as widely developed as the genetic literature on ADHD, there is a growing body of research implicating genetic influences in the aetiology of BPD. There is evidence to support familial aggregation of BPD features (Gunderson, Zanarini, et al., 2011; Zanarini et al., 2004) and findings from twin studies report heritability estimates in the range of 35%-67% (Distel et al., 2010; Reichborn-

Kjennerud et al., 2013; Torgersen et al., 2012). There is consensus between the studies that the remaining variance may be explained by unique rather than shared environmental influences, similar to ADHD.

To date there have been two GWAS studies of BPD. One study dimensionally assessed two Dutch cohorts (n= 7125) using the Personality Assessment Inventory-Borderline Features Scale and found a promising signal on chromosome-5, which corresponds to SERINC5, a protein involved in myelination (Lubke et al., 2014). Seven single nucleotide polymorphisms (SNP) in this region had *p*-values between $3.28x10^{-6}$ and $8.22x10^{-7}$, which are suggestive findings, but still fall below genome-wide levels of significance (Lubke et al., 2014). The other more recent and also first case-control GWAS study was performed in 998 BPD patients and 1545 psychiatric controls (Witt et al., 2017). While gene-based analysis yielded two significant genes for BPD, DPYD on chromosome 1 ($1.20x10^{-6}$) and PKP4 on chromosome 2 ($8.24x10^{-7}$), no genome-wide significant association was found for any SNP (Witt et al., 2017). To date, these specific findings in BPD do not overlap with the findings from ADHD.

1.5.5.3 Common genetic risk factors for BPD and ADHD

Though there is evidence for symptom overlap between the two disorders, to date only one study has explored whether this could reflect overlapping genetic influences. Using a population twin sample, a high phenotypic correlation (r = 0.59) was estimated between ADHD symptoms and borderline personality traits; consisting of four subscales - affective instability, identity problems, negative relationships and self-harm (Distel et al., 2011). The authors found that the phenotypic correlation was explained by 49% genetic factors and 51% environmental factors, suggesting that shared aetiology could be a cause of comorbidity between ADHD and BPD traits (Distel et al., 2011). No further studies have been reported to date, although the availability of GWAS means that the data to estimate the genetic correlation between the two disorders from SNP data is now available.

Overall, twin studies of ADHD and BPD show a similar pattern of genetic versus environmental influences, with slightly higher heritability estimates in most ADHD

studies. Yet it is important to note that heritability is also a function of the reliability of the measures being used, with the residual non-shared environment including measurement error. Heritability estimates from self-reported scales of symptoms are similar for ADHD and BPD (Brikell et al., 2015; Distel et al., 2010). Although for both ADHD and BPD there is no evidence for a main effect of shared environment (environmental effects shared by co-twins that explain co-twin similarity), shared environment may still play a major role through gene by environment interactions. It is therefore likely that for both disorders there are genetically-driven individual differences in susceptibility to environmental stressors. The relatively high genetic correlation between ADHD and BPD is based on the correlation of trait scores in the general population, rather than diagnosed cases, but suggests a considerable degree of underlying shared aetiology that may explain the frequent co-occurrence of ADHD and BPD. Further studies are needed to investigate the genetic overlap between the two disorders, but also the overlap with specific symptom domains such as emotional dysregulation.

1.6 Treatment approaches

1.6.1 Pharmacological

Treatment approaches to ADHD and BPD are widely divergent. According to evidence-based clinical guidelines, in BPD there is limited evidence that medications reduce borderline personality symptoms, including emotional dysregulation, and psychological treatments are the cornerstone of treatment (NICE, 2009). In contrast, in ADHD, there is good evidence for effects of medication on reducing ADHD symptoms (Faraone & Glatt, 2010; Meszaros et al., 2009; Spencer et al., 2005) and emotional dysregulation (Lenzi, Cortese, Harris, & Masi, 2017; Moukhtarian, Cooper, Vassos, Moran, & Asherson, 2017), and only limited evidence for effects of psychological treatments (NICE, 2008).

Clinical trials support the safety and efficacy of stimulants (methylphenidate, dexamphetamine, lisdexamfetamine) and atomoxetine, with reductions in the ADHD symptoms of inattention, impulsivity and hyperactivity, with moderate to large effect sizes ranging between .4 and .7 in adults (Castells, Ramos-Quiroga, Bosch, Nogueira, & Casas, 2011; Castells, Ramos-Quiroga, Rigau, et al., 2011;

Cunill, Castells, Tobias, & Capellà, 2013; Koesters, Becker, Kilian, Fegert, & Weinmann, 2009). Pharmacological treatments have been found to improve quality of life and daily functioning in addition to ADHD symptoms (Surman, Hammerness, Pion, & Faraone, 2013). In addition, several randomised controlled trials (RCT) have evaluated the effects of pharmacological treatments on emotional dysregulation in ADHD patients, and found comparable treatment responses to the primary symptoms of the disorder (Reimherr et al., 2005; Rosler et al., 2010; Wender et al., 2011). These findings are further validated by the results of two recent meta-analyses that found moderate effects of stimulants (methylphenidate, dexmethylphenidate, amphetamines, lisdexamfetamine) and atomoxetine on emotional dysregulation in ADHD (average Cohen's d across studies was around 0.4) (Lenzi et al., 2017; Moukhtarian et al., 2017). In these studies, emotional dysregulation was assessed with various measures including emotional dysregulation subscales of the Wender Reimherr Adult Attention Deficit Disorder Scale, the Behaviour Rating Inventory of Executive Function, the Conner's Adult ADHD Rating Scales and the Brown Attention Deficit Disorder Scale.

1.6.2 Non-pharmacological treatments

In contrast to treatment of ADHD, psychotherapy is regarded as first line treatment for people with BPD (American Psychiatric Association, 2013). The most common therapies are Dialectical Behaviour Therapy (DBT) (Lynch, Trost, Salsman, & Linehan, 2007), Transference-focused Therapy (Kernberg, Yeomans, Clarkin, & Levy, 2008), Schema Therapy (Kellogg & Young, 2006), Mentalization-based Treatment (Bateman & Fonagy, 2010), Systems Training for Emotional Predictability and Problem Solving. DBT is the most intensively studied intervention for BPD, and has been shown to significantly reduce anger (standardized mean difference (SMD = -0.83) and self-harm (SMD= -0.54), and improve overall mental health functioning (SMD= 0.65) (Kliem, Kroger & Kosfelder, 2010; Stoffers-Winterling et al., 2012). Not only is psychotherapy regarded as first line treatment for BPD, UK NICE guidelines stipulate that pharmacological treatments should not be used for managing BPD, nor for individual symptoms or behaviours associated with the disorder (NICE, 2009). The guidelines recommend the use of pharmacotherapy only as a short-term treatment

measure during a crisis or in the instance of co-occurring mental health disorders (NICE, 2009).

Currently, there is insufficient data on the treatment of co-occurring BPD and ADHD. With regard to drug treatment, there have been no RCTs of stimulants or atomoxetine in BPD alone or in co-occurring ADHD/BPD cases (Moukhtarian et al., 2017).

There have however been only two uncontrolled case reports (Hooberman & Stern, 1984; Van Reekum & Links, 1994) of successful methylphenidate treatment in patients with co-occurring BPD and ADHD, and two open-label studies (Golubchik, Sever, Zalsman, & Weizman, 2008; Prada et al., 2015). In one adolescent female-only study, patients with co-occurring ADHD and BPD (n=14) reported significant improvement of BPD symptom severity (SMD= -1.5) and aggressive impulsive behaviour (SMD= -1.31) following treatment with methylphenidate for 12 weeks (Golubchik et al., 2008). In a four-week study of 47 adults looking at effects of methylphenidate in addition to DBT, comorbid ADHD/BPD patients who were on stimulant medication (n=24) showed a statistically significant improvement in anger control (SMD= 0.14), motor impulsiveness (SMD= -0.62), depression (SMD= -1.09) and ADHD severity (SMD= -0.5), compared to those without medication (n=23) (Prada et al., 2015).

Similarly, there are various psychotherapeutic treatments available for adults with ADHD, who are either unresponsive to stimulants and/or atomoxetine, or in need of adjunctive psychotherapy. There have been two exploratory open label studies (Hesslinger et al., 2002; Philipsen et al., 2007) examining effects of psychotherapy in adult ADHD. According to the multicentre open label study of 72 patients with ADHD, an adaption of DBT, addressing emotion regulation, depression, impulse control, stress management, neurobiology of ADHD and ADHD in relationships, DBT has a therapeutic benefit for people with ADHD (Philipsen et al., 2007). There was a statistically significant decrease on all psychometric measures in the study after DBT treatment; SMD= -.74 for the ADHD-Checklist, SMD= -.5 for the Beck Depression Inventory (BDI) and SMD= -.34 for the adapted Symptom Check List (SCL-16) measuring agitation, disorganised behaviour, emotion dysregulation and irritability among other traits (Philipsen et al., 2007). Similarly, in the open

label pilot study of eight patients with ADHD, an adaption of cognitive behavioural therapy led to improvement in the same psychometric elements listed above; ES= .99 for the BDI, ES= 2.22 for the ADHD-Checklist and ES= 1.35 for the SCL-16 (Hesslinger et al., 2002).

There have been three RCTs testing the effectiveness of cognitive therapy for ADHD (Hirvikoski et al., 2011; Safren et al., 2005; Stevenson, Whitmont, Bornholt, Livesey, & Stevenson, 2002) with relatively small sample sizes (n=31, n=43 and n=51 respectively). These trials have attempted to investigate the effects of psychotherapy (in conjunction with medication in some cases) in adult ADHD on severity of ADHD symptoms (.57< d <1.7), depression, anxiety, anger control and organisation skills among other outcomes. More recently, a large multicentre RCT (n=433) has tested the effectiveness of tailored group psychotherapy versus clinical management (CM) reflecting optimal usual clinical care, with both groups randomised to methylphenidate or placebo (Philipsen et al., 2015). While methylphenidate significantly reduced ADHD symptoms compared to placebo (p=.003), there were no significant differences in ADHD symptoms for those receiving tailored group psychotherapy or CM (p=.160). In fact, in this trial, medication proved to be superior to intensive behavioural therapy, yet the latter resulted in better outcomes when combined with medication as compared to placebo (Philipsen et al., 2015).

Overall, while DBT modules and other systematically tailored psychotherapies appear to be helpful in ADHD, it is not yet clear whether they improve the core symptoms of ADHD (inattention, and hyperactivity/impulsivity), and there is insufficient data reported for effects on emotional dysregulation in ADHD (Corbisiero, Stieglitz, Retz, & Rosler, 2013; Hesslinger et al., 2002; Hirvikoski et al., 2011; Philipsen et al., 2015; Philipsen et al., 2007; Safren et al., 2005; Stevenson et al., 2002). This needs further investigation, since the evidence to date is based on relatively small samples, and there has been only one trial of cognitive behavioural therapy in ADHD samples without concomitant medication (Philipsen et al., 2015).

Clinical Implications

In clinical practice, it should be acknowledged that the co-existence of ADHD with BPD will complicate the diagnostic process, and hinder treatment outcomes. Currently, patients with co-occurring ADHD and BPD are often seen by different specialists and provided treatments for one condition or the other, but only rarely for both. In fact, there is a lack of empirical data to guide future clinical practice. Beyond the issues of differential diagnosis, there is insufficient awareness within specialist ADHD and BPD services of the potential benefits of treating the other condition. This needs to be addressed because treatment of both conditions may have positive benefits for individuals with overall better control of ADHD and BPD related symptoms and behaviours. Indeed, open clinical trials indicate the value of such a dual treatment approach.

Commonly in BPD patients with co-occurring ADHD, inattention and so called executive function deficits (i.e. sustained attention, forgetfulness, planning, organising, working memory), as well as physical restlessness and impatience, lead to difficulties in commitment and adherence to psychological therapies (Matthies & Philipsen, 2014). For example, this could be manifested in difficulties remaining seated, feeling restless and impatient, difficulties focusing on conversations and retaining information during therapy sessions, or insufficient planning and organisation to regularly attend therapy sessions (Matthies & Philipsen, 2014).

A further potential benefit in a subpopulation of individuals with co-occurring ADHD and BPD may be a reduction in emotional dysregulation and impulsivity following medication treatment of ADHD. Similarly, psychotherapeutic interventions may be helpful for ADHD cases with high levels of emotional dysregulation with partial or no response to ADHD drug treatments, which could be accounted for by BPD.

An important question arising from the literature is the specificity of emotional symptoms that are seen in both ADHD and BPD. However, symptoms reflecting dysregulation of emotional responses are also seen in other mental health disorders. A recent ESM study examined the dynamics of affective instability in patients with BPD compared with post-traumatic stress disorder and bulimia nervosa (Santangelo

et al., 2014). Using the same ESM protocol, all three conditions showed a similar degree of heightened affective instability regarding both the valence of emotional changes, and the level of associated distress (Santangelo et al., 2014). Although BPD is the only disorder for which emotional dysregulation is part of the core diagnostic criteria (American Psychiatric Association, 2013), it is possible that the emotional dysregulation present in individuals with BPD may be qualitatively distinct from that seen in other clinical groups, particularly in individuals with ADHD.

Given the emerging genetic findings in relation to ADHD and BPD, and the overlap of symptoms such as emotional dysregulation, there may be gains from comparing the neuro-cognitive underpinnings for ADHD and BPD, as well as overlapping symptom domains such as emotional dysregulation. At this stage, clinical trials are needed to evaluate the role of both ADHD medication and psychotherapy in the treatment of comorbid ADHD/BPD, and to identify treatment prognostic indicators.

1.7 Aims and outline of this thesis

This chapter reviewed the clinical profiles of ADHD and BPD. It also highlighted several areas in which further research is needed. Although it is beyond the scope of the current thesis to address all of these, an attempt will be made to shed light on several key issues raised. The overall aim of this thesis is to further our understanding of the phenotypic association between ADHD and BPD in adulthood, using a case-control design. Data presented in chapters three, four and five are from the Personality Research in ADHD and Emotional Instability (PRIDE) study. The overarching aim of these studies was to investigate whether symptoms of BPD and ADHD could be used to distinguish between the two disorders.

Chapter 2 provides a detailed description of the sample and methodology used in the PRIDE study.

In **chapter 3**, latent class analyses are undertaken to identify mutually exclusive classes of female ADHD and BPD subjects with homogeneous symptom profiles,

based on an empirical analysis of the data rather than using pre-determined DSM-5 diagnostic criteria. The latent classes are then compared against the clinical groups based on DSM classification, and differences in symptom profiles are explored across both DSM-5 clinical groups and latent classes.

Chapter 4 examines the association of mind wandering with ADHD and BPD. Although excessive mind wandering has been reported in the ADHD literature, there is limited prior data using ESM in daily life, and inattentiveness has been largely overlooked in the BPD literature. I address the question of whether patterns of mind wandering can be used to distinguish ADHD from BPD.

In **chapter 5**, using a similar ESM approach, I investigate the role of emotional dysregulation in the differentiation of adult females with ADHD and BPD using ESM. The main question addressed is whether the pattern of emotional symptoms is similar or different in patients with ADHD and BPD and could therefore be used to distinguish the two conditions.

In **chapter 6**, I present the results of a systematic review and meta-analysis examining the effects of stimulants and atomoxetine on emotional dysregulation in adults. This is a key question, as the findings could potentially be used to support the investigation of ADHD medications in the treatment of emotional dysregulation in other disorders that overlap with ADHD, including BPD.

Finally, in **chapter 7**, all the studies presented in this thesis are integrated and a critical discussion highlighting the clinical implications of the findings along with suggestions for future directions presented.

Chapter 2: Methods

2.1 Aim of this chapter

All data presented in the following three chapters (Chapters 3, 4 and 5) is drawn from the PRIDE (Personality Research in ADHD and Emotion instability) study. The specific aim of this chapter is to provide an overview of the methodologies used including study design, recruitment procedure, research assessment tools, and testing procedure.

Although most measures used in the study are outlined in this chapter, these are not exhaustive, but limited to those which are used in the studies reported in this thesis. Additional questionnaire and experimental data not reported here will be incorporated into publications at a later date.

2.2 Study overview

2.2.1 Location of study, funding and ethical approval

The PRIDE study was conducted at the Social, Genetic and Developmental Psychiatry (SGDP) Centre at the Institute of Psychiatry, Psychology and Neuroscience in conjunction with several National Health Service Trusts. The study was funded by Professor Philip Asherson's departmental research support account (PAD-9122). Research ethics approval for this study was granted by the National Research Ethics Service Committee London – London Bridge (reference: 15/LO/1280). Full informed consent was given by all subjects participating in the study.

2.2.2 Design

The study was a multi-centre case-control study, which included three clinical groups and one psychiatrically healthy control group. The study consisted of one 3-hour research assessment session, followed by 5-day experience sampling assessments (see section 2.4.3).

2.3 Recruitment

Since the main aim of the PRIDE study was to investigate similarities and differences in attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD), care was taken to ensure that confounding psychopathologies would not compromise the interpretability of results. Therefore, strict exclusion criteria were applied to all study groups to ensure that differences between participants with and without ADHD and BPD would not reflect co-occurring psychiatric illnesses, psychoactive medication, neurological conditions or substance abuse problems.

2.3.1 Inclusion and exclusion criteria

Eligible participants were female adults aged 18-65 years. They had either an established (a pre-existing diagnosis by a clinician) or working/research (previously undiagnosed patients) diagnosis of ADHD, BPD or comorbid ADHD/BPD according to the Diagnostic and Statistical Manual of mental disorders (DSM) definitions of the disorders.

Exclusion criteria for the clinical and control groups were: male gender; not fluent in English (to understand or answer detailed questions about mental health symptoms); history of bipolar I and II, recurrent depressive episodes, and schizophrenia; current Axis I disorders; head injury that have caused long-term neurological and behavioural problems; IQ<70 (assessed during the research session); and current treatment with mood stabilisers and/or anti-psychotics. Participants on stimulant medication for ADHD were asked to come off this medication for 48 hours before the baseline assessment and the following five days during the experience sampling assessments (see section 2.4.3). Due to the frequent drug and alcohol use in ADHD (Bernardi et al., 2012; Fayyad et al., 2007; Kessler et al., 2006) and BPD (Fyer, Frances, Sullivan, Hurt, & Clarkin, 1988; Zanarini et al., 1998) populations, I excluded individuals with addiction disorders, but not for elevated alcohol and drug use (see section 2.4.1.6).

2.3.2 Recruitment sources

2.3.2.1 Control participants

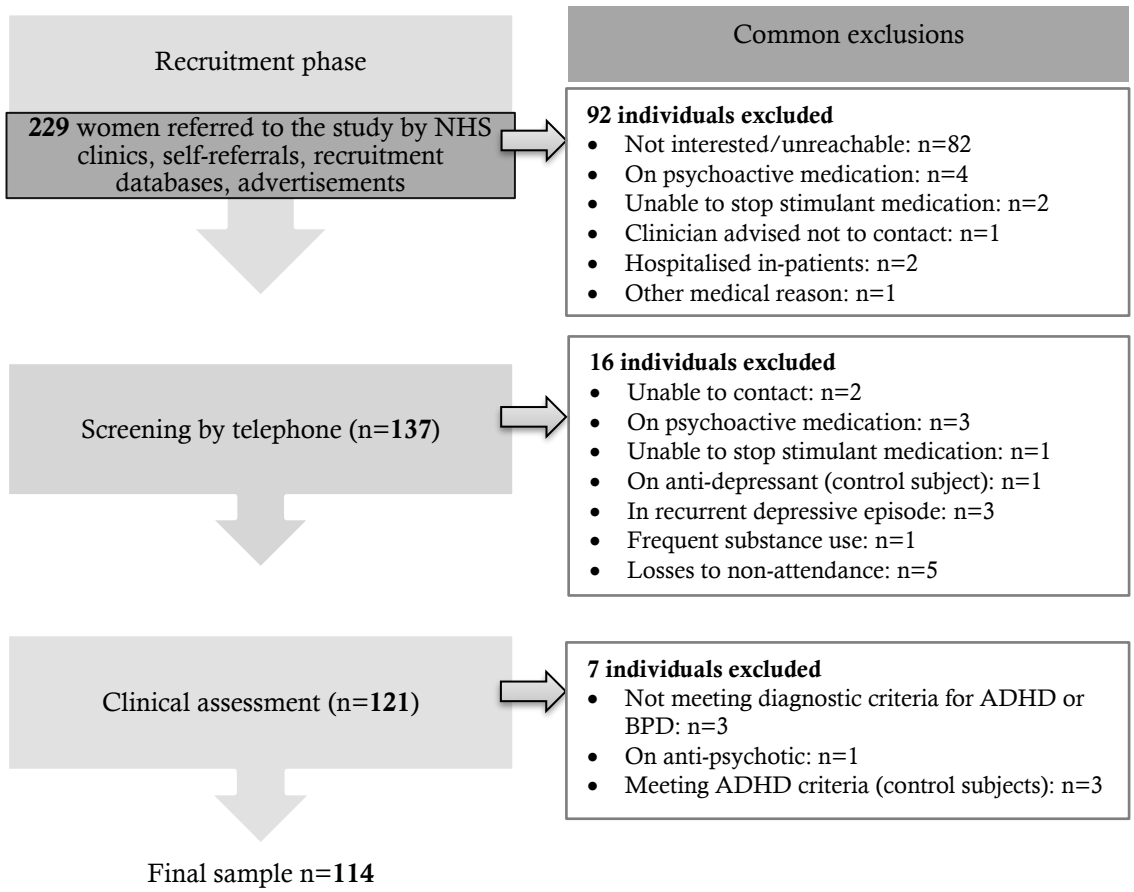
Control subjects, not meeting criteria for ADHD or BPD, were recruited from volunteer databases held at the SGDP, King's College London, and through advertising around the university and within the local community (e.g. community centres, supermarkets). Initial contact was made by post, email, or telephone. Those who expressed an interest in participating in the study underwent a structured telephone screening (Appendix 1) of exclusionary criteria, which involved detailed questions assessing previous or current neurological problems, mental health problems (including presence, treatment for or diagnosis of anxious, depressive and manic/hypomanic symptoms), and drinking and drug *use* habits. If deemed suitable following the telephone screening, they were then booked in for a research assessment.

2.3.2.2 Clinical cases

Recruitment of clinical cases occurred through seven sources, of which five were the following NHS trusts: South London and Maudsley NHS Trust, Camden and Islington NHS Trust, Northamptonshire NHS Trust, Leicestershire NHS Trust and West London Mental Health NHS Trust. The research team regularly attended the clinical team meetings at these NHS trusts to communicate the study to members of the healthcare team. Members of the clinical team identified suitable participants from their services. Those deemed eligible based on the study's exclusion/inclusion criteria were either given in person or sent by email/post study information sheets, a response slip and a stamped addressed envelope by clinicians with the help of a member of the PRIDE research team (TRM, DW, KW, JP or RM) who held honorary clinical contracts or research passports with the trusts. Where no response slip was returned, participants were contacted by telephone to determine their interest in participating. Those who expressed an interest in participating in the study underwent a structured telephone screening (Appendix 2) of exclusionary criteria by telephone. If deemed suitable following the telephone screening, they were then booked in for a research assessment.

Recruitment was also done through databases of participants who took part in previous studies at the SGDP and consented to be contacted again for future studies, in addition to self-referrals through advertisements in certain clinics, charities and public community spaces (e.g. library, community centres). Initial contact in these cases was done by members of the research team (TRM, DW, KW, JP or RM) by post, telephone or email, followed by the same procedure outlined above.

Figure 2.1 Flow diagram of recruitment and exclusions



2.3.3 Sample

2.3.3.1 Clinical diagnosis

Clinician diagnoses were based on DSM criteria for ADHD and BPD (American Psychiatric Association, 2013), and validated for research by members of the research team.

ADHD symptomatology was assessed using the Diagnostic Interview for ADHD in Adults (DIVA). The DIVA is a validated structured interview for the assessment of adult ADHD according to DSM-IV diagnostic criteria. It consists of 18 questions (nine relating to inattentive symptoms and nine to hyperactive/impulsive), scoring the presence/absence of DSM-IV symptoms during both childhood and adulthood (Kooij, 2013). Symptom onset and chronicity was established before the age of 12 (by the presence of "several" symptoms, defined as three or more in the PRIDE study) and the presence of more than five symptoms of inattention or hyperactivity/impulsivity in adulthood (in accordance with DSM-5 criteria; American Psychiatric Association, 2013; Kooij, 2013). They met all other criteria for DSM-5 ADHD including pervasive impairments from the symptoms in more than one setting.

BPD diagnosis was established by the presence of a pervasive pattern of instability of interpersonal relationships, self-image and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the nine diagnostic symptoms for the disorder in accordance to the DSM-5 (Association, 2013; First, Gibbon, Spitzer, Williams, & Benjamin, 1997). BPD symptomatology was assessed using the Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD). The ZAN-BPD is a semi-structured interview that generates a continuous measure assessing borderline psychopathology (Zanarini, 2003). Each of the nine items is rated on a five-point anchored rating (0=no symptoms to 4=severe symptoms), yielding a maximum score of 36. The ZAN-BPD has high internal consistency (Cronbach's α=.85) and significant test-retest reliability (p< .001). The ZAN-BPD was used as a proxy for BPD diagnostic criteria: a symptom was marked as present if an item had a score of two or above, which is equivalent to being rated as 'threshold or true' on the Structured Clinical Interview for DSM-IV (SCID-II) BPD criteria (First et al., 1997). Therefore, a BPD research diagnosis was established when a participant had a score of two or above on at least five of the nine items on the ZAN-BPD.

2.3.3.2 Participants

As shown in the recruitment flow diagram (see Figure 2.1), a total of 114 adult females were recruited, including 32 with ADHD (M_{age}= 36.94, SD= 11.54), 19 with BPD (M_{age}= 35.37, SD= 11.39), 27 with comorbid ADHD/BPD (M_{age}= 32.81, SD= 13.18) and 36 psychiatrically healthy control participants (M_{age}= 29.44, SD= 8.29).

2.4 Research assessment tools

The following is an overview of the measures used during the testing session.

2.4.1 Rating scale measures

All participants completed a number of measures of everyday symptoms and problems during their appointment and at home prior to their assessment.

2.4.1.1 Emotional dysregulation

Three questionnaires were used to measure emotional dysregulation.

The self-rated Affective Lability Scale-Short Form (ALS-SF) (Oliver & Simons, 2004), comprised of 18 items scored 0-3 (very un-descriptive, rather un-descriptive, rather descriptive, very descriptive), measures swift fluctuations from normal (euthymic) mood to other emotional modalities including elation, depression, and anger (Appendix 3). Previous factor analysis confirmed good fit for three domains in the ALS-SF: Anxiety-Depression, Depression-Elation and Anger (Oliver & Simons, 2004). Total overall score was used as an outcome variable.

The Affective Reactivity Index (ARI) measures chronic irritability, defined as a mood of easy annoyance and touchiness characterised by anger and temper outbursts (Stringaris et al., 2012). It contains six symptom items and one impairment item about irritability (Appendix 4). The ARI has shown good internal consistency and factorial structure across both clinic and community-based samples (Stringaris et al., 2012).

The Wender-Reimher Adult Attention Deficit Disorder Scale- Emotional dysregulation subscale (WRAADDS-EDS) (Wender, 1995), was administered as an interviewer-rated measure to assess temper, affective lability and emotional over-reactivity (Appendix 5). The WRAADDS shows high internal consistency (Cronbach's α= .78) and good test-retest reliability (r= .96) (Wender, 1995).

2.4.1.2 Mind wandering

Self-reported excessive mind wandering was assessed using the Mind Excessively Wandering Scale (MEWS) (Mowlem et al., 2016). It consists of 15 items rated on a 4-point Likert-scale (0=not at all to 3=nearly all the time or constantly) (Appendix 6). The MEWS in adults with ADHD shows good internal consistency (α > .9), and high sensitivity (.9) and specificity (.9) (Mowlem et al., 2016).

2.4.1.3 Functional impairment

Impairment in major life domains was assessed using the Weiss Functional Impairment Rating Scale-Self-report (WFIRS-S), which measures impairments in several everyday situations (Appendix 7). These include impairments in the areas of family, work, social function, life skills (e.g. managing money, hygiene, appearance, sleep, health), self-concept (e.g. feeling about oneself, incompetent) and risk-taking behaviours (e.g. drug taking, drinking, aggressive behaviour, illegal actions, sexually risky behaviours).

2.4.1.4 Childhood maltreatment

The Childhood Trauma Questionnaire (CTQ) is a 28-item self-report questionnaire that measures five categories of childhood trauma experience; emotional, physical, and sexual abuse, and emotional and physical neglect (Appendix 8). Reliability for the CTQ is good with high internal consistency scores. Factor analysis tests on the five-factor CTQ model showed structural invariance, which demonstrates good validity (Bernstein & Laura, 1998).

2.4.1.5 Co-occurring depressive and anxious symptomatology

Co-occurring depression and anxiety was measured by the Brief Symptom Inventory (BSI) (Derogatis, 1993). The BSI is a self-rated measure consisting of 53-items evaluating psychological distress and psychiatric disorders in nine domains including depression and anxiety on a 4-point Likert-scale (0=not at all to 3=extremely) (Appendix 9). The BSI has good internal reliability of .7 and robust test-retest reliability of .68 (Derogatis, 1993).

2.4.1.6 Alcohol and drug use

The following two self-report measures (Appendix 10) were administered to check for drug and alcohol use and were not used as outcome measures in subsequent analyses. Possible alcohol dependence in the last 12 months (i.e. a score of 20 and above) was assessed by the Alcohol Use Disorders Identification Test (AUDIT-C), an alcohol screen that can help identify individuals who are hazardous drinkers or have active alcohol use disorders (abuse or dependence). It was scored on a scale of 0 (no alcohol use) to 4 (daily or almost daily) (WHO, 2001). Frequent drug use in the last 12 months (i.e. use of recreational drugs several times a week or more) was assessed by the Substance Use Checklist (SUC v.1.1), a short screen to identify patterns of illegal drug use in the past 12 months measured on a scale of 0 (never used) to 5 (several times a day).

2.4.2 Intellectual function

Intellectual function was assessed using the Wechsler Abbreviated Scale of Intelligence- Second edition (WASI-II). Two subtests (vocabulary and matrix reasoning) of the WASI-II were administered to derive an estimate of IQ (Wechsler, 2011).

2.4.3 Experience sampling assessments

2.4.3.1 Rationale

Although rating scale and interview measures are frequently used in psychiatry, extensive research has now highlighted limitations of retrospective recall. Of

particular note is research that identifies different recall biases in psychiatrically ill and healthy populations (Ebner-Priemer et al., 2006; Taylor & Brown, 1988). These methodological problems can be overcome by observational studies, in which a behaviour is elicited and coded, or prospective longitudinal data collection measures, such as in experience sampling assessments. Experience sampling method (ESM), also called ecological momentary assessment, involves repeated assessments over time, where series of immediate reports can be statistically summarised to obtain indices of daily experience without relying on participant's memory (Trull et al., 2008), resulting in reduced systematic and random sources of measurement error, increased ecological validity and reliability (Bolger, Davis, & Rafaeli, 2003), and enhanced generalisability of findings (Ebner-Priemer & Trull, 2009). Specifically, this methodology lends itself to the investigation of instability or change in certain behaviours, which can be measured directly from one moment to another in everyday life.

2.4.3.2 Methodology

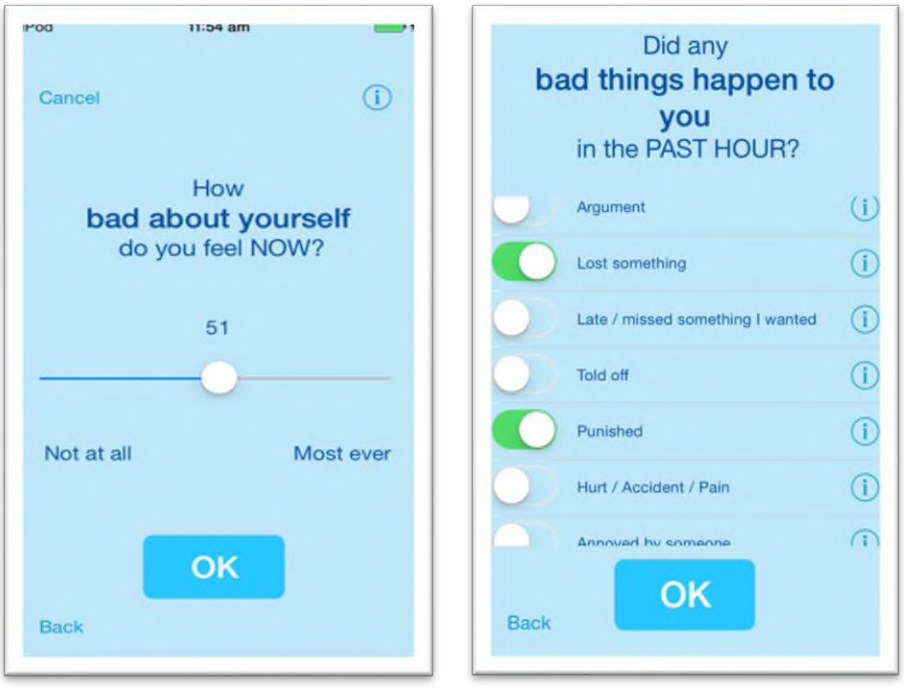
Experience sampling was carried out using an iOS app called MoodMapper, designed for the investigation of emotional dysregulation and mind wandering by Dr. Celine Ryckaert and Professor Philip Asherson. MoodMapper was uploaded onto Apple iPods with all other functions disabled. Participants started the ESM phase the day after their research appointment for five consecutive days. Signals for the onset of each monitoring period was provided by Vibralite 12 wristwatches that were synchronised with the iPods giving silent vibration signals eight times a day, at the onset of each rating period. Participants were instructed to complete each rating based on the time-period just before the signal. Following the protocol of Skirrow and colleagues (Skirrow et al., 2014), signals occurred following a pseudorandomised schedule, with a minimum inter-rating interval of 65 minutes and a maximum interval of 135 minutes (around 10 hours of data collection each day). Start and end times were the same each day.

In ESM research other response schedules are also widely used, such as fixed response schedules (Ebner-Priemer et al., 2006), schedules which include a fixed number of random prompts within specific time periods of a day (Solhan, Trull,

Jahng, & Wood, 2009), and schedules which include a fixed period of reassessment with a shorter random interval (e.g. every hour, with a 5-minute random interval (Hoeksma, Oosterlaan, & Schipper, 2004). Since the equipment used in this study did not allow for the programming of a randomised response schedule, a pseudorandomised, fixed schedule was adopted. This was to facilitate data collection that would not be anticipated by the participants, and to enable capture data whilst participants were engaging in their normal everyday activities.

MoodMapper employed continuous analogue scale questions or multiple-choice questions (see Figure 2.2 for examples). On questions regarding mood and frequency of mind wandering (e.g. "How frustrated do you feel NOW?", "How much is your mind on what you are doing or elsewhere NOW?"), participants responded on a numerical scale, with ratings ranging from 0 (not at all) to 100 (extremely). Additionally, content and awareness of mind wandering, as well as good or bad experiences that had occurred to participants during the hour preceding each monitoring period (e.g. "Did any good things happen to you in the PAST HOUR?"), were assessed by multiple-choice questions. Details of each item used in the ESM analyses are presented in subsequent chapters (i.e. mind wandering items in chapter 4 and emotion items in chapter 5).

Figure 2.2 Examples of MoodMapper questions



2.4.3.3 Compliance rates

To reduce the likelihood of participant bias from self-selection of monitoring instances, all reports not completed within 16 minutes after the vibration signal were excluded from analysis. Allowing a choice in the self-selection of monitoring instances runs the risk of introducing each participant's bias in selecting some instances and overlooking others (Bolger et al., 2003). Compliance rates for each participant were obtained by identifying the proportion of monitoring instances completed within the 16-minute window.

Several steps were implemented to promote compliance and were incorporated into the testing protocol, including telephone calls to prompt participants when they were required to start monitoring, a follow-up call during the monitoring week, providing a 'mood monitoring hotline' telephone number and e-mail address, and an instruction leaflet. Overall compliance was satisfactory across the whole sample with a mean of 74.8% and SD of 14.9.

2.5 Testing procedure

2.5.1 Initial contact

Throughout the recruitment process, a strong emphasis was placed on the voluntary nature of research participation and ensured full informed consent before individuals took part in the study. The study was designed in such a way that for cases from clinics, participation would not result in interference with or impact adversely on the nature or quality of the clinical care they received.

Potential clinical participants were approached face to face by a member of the clinical care team who briefly explained what the study is about, handing over a patient information sheet, and asked if they are willing to have their personal details passed onto a member of the research team. Alternatively, potential suitable participants identified through the clinics' databases received an invitation letter along with the information sheet, to which they could have responded with their details in the post or via email, by a member of the clinical care team. Those who did not respond to the initial correspondence within two weeks, were contacted by

telephone to ask whether they received the information, had any questions and would be interested to take part in the study. Once permission was granted by a potential participant, their contact details were passed on to the research team by members of the clinical care team.

For potential participants who had taken part in previous similar studies at the SGDP centre, their consent forms were thoroughly checked to make sure they had given prior consent to be contacted again in the future, and were then contacted by telephone, post or email to briefly explain what the study was about and check whether they would be willing to participate.

Control volunteers, self-referred participants through advertisements or word of mouth made initial contact to the research team to enquire further about the study. Once a brief summary was given, they were also sent an information sheet and a response slip.

2.5.2 Telephone screening

Once the research team was given permission from the clinical care team to contact individuals or had received confirmation from self-referred or previous volunteers, a follow-up call was arranged, and exclusion and inclusion criteria were checked. During the telephone call, the project was briefly summarised again, and individuals were given the opportunity to ask any questions they may have before proceeding to the screening phase.

All individuals who agreed to proceed to the screening phase were told that information collected during the call will be kept confidential and no data will be used until the participant attends the research appointment and signs a consent form. All subjects then underwent structured telephone screening (Appendix 1 and Appendix 2).

2.5.3 Research assessment

Those not excluded after the telephone screening were invited for an assessment. Participants were sent a letter by post, confirming their agreed appointment date, time and location, in addition to a questionnaire booklet, which included the ALS,

WFIRS-S, CTQ and MEWS (see section 2.4.1 for details of each measure). Participants were asked to complete these and bring them along when attending their appointment. Participants were also asked to refrain from drinking caffeine and consuming alcohol on the day of the study and during the preceding night. Instructions to this effect were included in the appointment confirmation letter and were also given by telephone during appointment reminders. ADHD cases on stimulant medication were also reminded to stop taking their medication for 48 hours before the assessment.

At the start of the assessment fully written informed consent was obtained. Participants first underwent IQ testing, then the clinical interviews, followed by the completion of four self-report questionnaires (BSI, AUDIT-C, SUC, ARI; see section 2.4.1 for details of each measure).

At the end of the testing session, participants were provided with the ESM equipment (iPod with MoodMapper app, vibrating wristwatch, as described in section 2.4.3, and an instruction leaflet), and were given full instructions and training for use. A postage paid envelope was provided for participants to return the equipment after completing their monitoring period.

All participants were compensated for their travel expenses. In addition, all were given a monetary incentive upon completion of their monitoring and the return of equipment; £50.

2.6 Preparatory work

2.6.1 Power calculations

Our aim was to detect clinically meaningful differences between groups. Given the exploratory nature of this study and novel methodologies used, there were no prior findings on which I could have based the power analyses. The statistical software G*Power 3.0 (Faul, Erdfelder, Lang, & Buchner, 2007) with power set at 80% and an alpha set at .05, showed that a sample size of 18 individuals per group, with four groups in total, is sufficient to detect effect sizes of .4.

2.6.2 Statistical analyses

For simple group comparisons, normality of data was assessed graphically by examining histograms and QQ plots, and with the Shapiro-Wilk statistic. Normal or transformed-normal data were tested using univariate ANOVAs. Data with skewed residual distributions that did not normalise with transformations were analysed using the Kruskal-Wallis test. Where appropriate, Bonferroni adjusted or non-parametric equivalent pairwise comparisons were conducted to discriminate which groups differed.

For the analysis of ESM data in chapters 4 and 5, multilevel models were used to take into account correlated observations nested within individuals, and *to* account *for differences in reporting rates* (individuals with a greater number of *valid reports* contribute more to the estimation of group means) (Jahng *et al.*, 2008). When a predictor varies between and within subject level over time, the coefficient for that predictor is a weighted average of the between and within subject relationships. It is therefore necessary to separate these variables by rescaling into their components at each level. In order to do this, a person-mean centering approach was used for all variables to be used as predictors, whereby the mean of a variable per individual across subject and time points was subtracted from each raw score of that variable (Bolger & Laurenceau, 2013). Moreover, observations from the same clusters or groups are usually more identical than observations from different clusters. And if they are similar, we can't use statistical paradigms that assume independence, because estimates of variance and consequently p values will be incorrect. Mixed models therefore take into account and give an estimate of the correlations in the same cluster (Aarts et al., 2014). When there is consistency among a cluster's responses, then there is variation among the clusters' means. This is the between-cluster variance. The ratio of the between-cluster variance to the total variance (the sum of between-cluster and within-cluster variability) is called the Intra-Class Correlation (ICC) (Heck & Thomas, 2015). I therefore calculated ICC for all outcome variables used in the ESM analyses (chapters 4 and 5), and found it to be between 30-80%, which is within the acceptable range (Aarts et al., 2014; Bolger & Laurenceau, 2013).

Multilevel models were adjusted using Bonferroni and Bonferroni-Holm corrections. I investigated group differences in a 2x2-model (ADHD*BPD, assuming non-additivity of the ADHD and BPD effects), followed by contrasts according to a priori hypotheses defined in each chapter.

Analyses in subsequent chapters were carried out using STATA (Version 15), SPSS (Version 24), SAS University edition- virtualbox and Mplus7.

Given the large number of subscales used in this study, and therefore the high number of statistical comparisons and associated risk of type-I error, all reported *p*-values were adjusted for multiple testing using family-wise Bonferroni corrections (detailed in subsequent chapters) to maintain $\alpha=.05$ for all independent tests employed in the primary analyses and all subsequent post-hoc comparisons.

2.6.3 Risks/ethical considerations

The study was designed in such a way that interruptions with daily routine were as limited as possible, reducing the burden associated with participation. More specifically, all assessments were grouped into only one research appointment, which was held at a location convenient for the participant (i.e. clinics or SGDP). The ESM phase was designed in such a way that disruptions to daily function were kept to a minimum (i.e. very short questioning sessions, discrete vibrating wrist watch to alert subjects, assessment covering only five days and normal waking hours). Participants with ADHD already being treated with stimulant medication were asked to stop their medication for the week of the ESM. This was an approach used in previous research (Skirrow et al., 2014). This was only done with the agreement of both the patient and the clinical care team. Short-term drug holidays are not uncommon in the clinical management of ADHD and enable patients to evaluate how well they are able to manage without their medication (Wilens, Morrison, & Prince, 2011). Patients were advised that they could restart medication regimens immediately if they felt this to be necessary or if they were advised to do so by the clinical care team.

Chapter 3: Overlapping symptoms in ADHD and BPD: A comparison of clinical profiles by DSM classifications and latent classes

3.1 Abstract

Attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) are frequently comorbid and have several overlapping symptoms. To contribute to a better understanding of the associations between ADHD and BPD, latent class analysis (LCA) was undertaken to identify mutually exclusive classes differing in profiles of adult symptoms of ADHD and BPD. First, the latent classes were examined in relation to the Diagnostic and Statistical Manual of mental disorder 5th edition (DSM-5) classification of ADHD and BPD. Second, the latent classes and DSM-5 groups were used to explore the sample's characteristics on different domains of psychopathology. LCA revealed an optimal solution with four distinct symptom profiles, mapping on well to the groups pre-defined by the DSM classification. All patients with BPD had some ADHD symptoms, and vice versa. This study's findings support the view that emotional dysregulation, mind wandering, anxiety, childhood maltreatment and impairments in various domains of everyday life reflect non-specific symptoms and outcomes that are seen across both disorders and cannot be relied upon to discriminate ADHD from BPD.

3.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD), characterised by developmentally inappropriate levels of inattention and hyperactivity/impulsivity (American Psychiatric Association, 2013), is a common neurodevelopmental psychiatric disorder, with symptom onset in childhood (American Psychiatric Association, 2013). ADHD persists into adulthood in around two thirds of childhood cases, with a prevalence in adults of around 2.5-4% (Fayyad et al., 2007; Kessler et al., 2006). Up to 78% of adults with ADHD present with other DSM-5 disorders such as mood and anxiety disorders, and substance-use disorders (Kessler et al., 2006; Wilens, Biederman, & Spencer, 2002), but relatively little attention has been given so far on the overlap of ADHD with personality disorders, notably borderline personality disorder (BPD).

BPD is a complex psychiatric disorder, that has a general population prevalence between 1.4% and 6% (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006; Grant et al.,

2008; Lenzenweger, Lane, Loranger, & Kessler, 2007), and around 20% within inpatient psychiatric settings (American Psychiatric Association, 2013; Grant et al., 2008). BPD is characterised by pervasive patterns of unstable interpersonal relationships, pronounced impulsivity, unstable identity, and difficulties with emotional dysregulation and anger control (American Psychiatric Association, 2013), substantially affecting one's quality of life and psychosocial functioning (Gunderson et al., 2011).

ADHD and BPD have many overlapping features, impulsivity and emotional dysregulation being the most apparent ones (Asherson et al., 2014; Moukhtarian, Mintah, Moran, & Asherson, 2018). These shared features of trait-like symptoms that characterise both ADHD and BPD make differential diagnosis challenging. Moreover, given the lack of validated objective biomarkers with sufficient specificity in clinical practice that would distinguish aetiologically distinct mental health conditions, it remains unclear whether ADHD and BPD reflect qualitatively distinct disorders, or overlapping syndromes (Vella, Aragona, & Alliani, 2000). Furthermore, the phenotypic and aetiological heterogeneity of both ADHD and BPD leads to difficulties in clearly defining which characteristics are related to the same underlying susceptibility, and which are not (van Dijk, Lappenschaar, Kan, Verkes, & Buitelaar, 2011).

To better understand the similarities and differences between ADHD and BPD, latent class analysis (LCA) was carried out on a sample of females selected for DSM-5 ADHD, BPD and comorbid ADHD/BPD, as well as healthy controls, to identify exclusive classes of subjects with homogenous symptom profiles related to ADHD and BPD. LCA is a statistical technique used for exploratory and hypothesis-generating purposes (McCutcheon, 1987). Exploration of symptomatology using this empirical approach has the major advantage of not losing valuable information (i.e. in the DSM classification those who score just below the diagnostic threshold are regarded as non-cases, whereas this may not be the case using LCA).

This empirical approach to classification was taken as the DSM-5 approach for both ADHD and BPD uses symptom count thresholds, which are to some extent arbitrary. Some cases fall just below DSM-5 symptoms thresholds and could

therefore be considered subthreshold to the full DSM-5 criteria, but still reflecting the same underlying disorder. The aim was to compare the DSM-5 classification of individuals to the LCA classification and apply both classification approaches to the investigation of symptoms and behaviours associated with both disorders.

The current study reports data from an adult female sample with DSM-5 ADHD, BPD, comorbid ADHD/BPD and a healthy control group. Participants were tested using validated rating scales and interviews of psychopathology. I specifically aimed to: (1) classify female patients with different profiles of adult symptoms of ADHD and BPD into homogenous subsamples; (2) examine the latent classes in relation to the DSM-5 classification of ADHD and BPD; and (3) compare ADHD and BPD on different domains of psychopathology, first using the clinical groups based on DSM-5 diagnostic classification and then the latent classes.

3.3 Methods

3.3.1 Sample

114 females aged 18-65 years participated in this study. Clinical cases were recruited from several ADHD and borderline personality specialist clinics in South and North London and the Midlands regions of England. Healthy controls were recruited from volunteer databases, and through advertisements in King's College London and within the local community. Recruitment is detailed in Chapter 2 (section 2.3).

The National Research Ethics Service Committee London – London Bridge, granted research ethics approval for this study (reference: 15/LO/1280). All subjects participating in the study gave full informed consent.

3.3.2 Diagnostic and symptom measures

ADHD and BPD were assessed by the Diagnostic Interview for ADHD in Adults (DIVA) and the Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD) respectively. For further details on diagnosis refer to section 2.3.3.1 in Chapter 2.

Emotional dysregulation was assessed using two self-rated questionnaires and one interview measure:

The self-rated Affective Lability Scale-Short Form (ALS-SF) (Oliver & Simons, 2004), comprised of 18 items scored 0-3 (very un-descriptive, rather un-descriptive, rather descriptive, very descriptive), measures swift fluctuations from normal (euthymic) mood to other emotional modalities including elation, depression, and anger (Appendix 3).

The Affective Reactivity Index (ARI) measures chronic irritability, defined as a mood of easy annoyance and touchiness characterised by anger and temper outbursts (Stringaris et al., 2012). It contains six symptom items and one impairment item about irritability (Appendix 4).

The Wender-Reimherr Adult Attention Deficit Disorder Scale- Emotional Dysregulation Subscale (WRAADDS-EDS), administered as interviewer-rated measure, assesses temper, affective lability and emotional over-reactivity (Wender, 1995) (Appendix 5).

Impairment in major life domains was assessed using the Weiss Functional Impairment Rating Scale-Self-report (WFIRS-S), which measures impairments in several everyday situations. These include impairments in the areas of family, social function, life skills (e.g. managing money, hygiene, appearance, sleep and health), self-concept (e.g. feeling bad about oneself, incompetent), and risk-taking behaviours (e.g. drug taking, drinking, aggressive behaviour, illegal actions, and sexually risky behaviours) (Appendix 7).

Anxiety and depression symptoms were assessed by the Brief Symptom Inventory (BSI) (Derogatis, 1993). The BSI is a self-rated measure consisting of 53-items evaluating psychological distress and psychiatric disorders in nine domains including depression and anxiety on a 4-point Likert-scale (0=not at all to 3=extremely). Given the significant co-occurrence of depressive and anxious symptomatology in both ADHD and BPD populations (Cumyn, French, & Hechtman, 2009; Zanarini, Gunderson, Frankenburg, & Chauncey, 1989),

excluding individuals presenting with these symptoms would have made our findings unrepresentative of the ADHD and BPD populations (Appendix 9).

Childhood maltreatment was assessed using the Childhood Trauma Questionnaire (CTQ), which is a 28-item self-report screening questionnaire measuring five categories of childhood maltreatment: emotional, physical, and sexual abuse, and emotional and physical neglect (Bernstein & Laura, 1998) (Appendix 8).

Intellectual function was assessed using the Wechsler Abbreviated Scale of Intelligence- Second edition (WASI-II). Two subtests (vocabulary and matrix reasoning) of the WASI-II were administered to derive an estimate of Intelligence Quotient (IQ) (Wechsler, 2011).

3.3.3 Statistical analyses

3.3.3.1 Latent class analysis

LCA was used as an empirical method to find the smallest number of groups of individuals (i.e., classes) with similar patterns of symptoms and classify them into homogenous sub-groups. Instead of using predefined criteria for the presence or absence of a disorder, LCA uses ratings of subjects on several symptoms and describes the probabilities of a set of observed categorical variables across groups of individuals. Individual differences in response patterns are explained only by differences in latent class membership, where each class shows a class-specific response profile (Geiser, 2010).

For this study, to identify distinct clinical subgroups, LCA was performed using 18 adult ADHD items (9 inattentive and 9 hyperactive/impulsive) from the DIVA (Kooij, 2013) and 9 BPD items from the ZAN-BPD (Zanarini, 2003) as class indicators. All items on the DIVA were scored as present or absent. Given that the ZAN-BPD is a continuous measure of borderline personality symptom severity (as explained in chapter 2 section 2.3.3.1) a symptom was marked as present if an item had a score of two or above, equivalent to 'threshold or true' on the Structured Clinical Interview for DSM-IV (SCID-II) BPD criteria (First, Gibbon, Spitzer, Williams, & Benjamin, 1997); otherwise was marked as absent.

Calculations were made with Mplus (Muthén & Muthén, 2006). Mplus provided several decision parameters of which the Bayesian Information Criterion (BIC) and the Akaike Information Criterion (AIC) likelihood ratio tests were used in the exploratory phase of the analysis, with lower numbers indicating a better fit. The BIC is a measure of the goodness of fit of a model that considers the number of parameters and the number of observations, whilst the AIC only considers the number of model parameters (Nylund, Asparouhov, & Muthén, 2007). The data were analysed with an increasing number of classes until there was no improvement in any of the decision criteria (i.e., lower BIC and AIC values). A small number of candidate models were thus identified for further analysis with the bootstrap likelihood ratio test (BLRT), relative entropy and interpretability. The BLRT, which is the most sensitive index to identify the correct number of classes, examines whether there is significant improvement in model fit when estimating k classes relative to the k − 1 class. The BLRT has better type I error and finds the right number of classes better than BIC (Nylund et al., 2007). The entropy of a model is a measure of classification uncertainty between 0 and 1, with values near one indicating high certainty in classification and values near zero indicating low certainty (Nylund et al., 2007). All analyses were run with several different starting values to minimise the influence of local extremes.

For the LCA model, 18 ADHD (9 inattention and 9 hyperactivity/impulsivity) plus 9 BPD variables were used, with a sample size of n=114. The class memberships were then compared to the original group membership (i.e. DSM-5 classification of ADHD only, BPD only or ADHD plus BPD, and controls).

3.3.3.2 Group comparisons

Analyses were completed in SPSS 24, with a nominal level of significance set at $p<.05$. Bonferroni correction was implemented where multiple comparisons were carried out. There were 18 different outcome measures, of which six were highly correlated (see Table 3.1). The Bonferroni adjusted *p*-value to account for multiple testing was therefore held at $p=.004$, accounting for 12 independent measures. Rating scale data were not normally distributed across the whole sample for all variables except IQ and total mean scores for the ALS, and therefore group

comparisons for all other variables were carried out using non-parametric Kruskal-Wallis tests[1], followed by Bonferroni adjusted post-hoc tests where appropriate.

Table 3.1 Pearson correlation coefficients between outcome measures

	BSI_Depression	**BSI_Anxiety**	**ARI**	**ALS**	**WRAADDS-EDS**	**MEWS**
BSI_Depression	-	0.8	0.7	0.7	0.7	0.6
BSI_Anxiety	0.8	-	0.7	0.8	0.8	0.7
ARI	0.7	0.7	-	0.7	0.8	0.7
ALS	0.7	0.8	0.7	-	0.8	0.7
WRAADDS-EDS	0.7	0.8	0.8	0.8	-	0.8
MEWS	0.6	0.7	0.7	0.7	0.8	-

All correlations are significant at the $p<.001$ level (2-tailed)
Note: BSI, Brief Symptom Inventory; ARI, Affective Reactivity Index; ALS, Affective Lability Scale; WRAADDS-EDS, Wender-Reimherr Adult Attention Deficit Disorder Scale- Emotional Dysregulation Subscale; MEWS, Mind Excessively Wandering Scale.

3.4 Results

3.4.1 Fit statistics and identification of the best fitting class solution

I estimated models with two through five latent classes of adult symptoms of ADHD and BPD. The BIC values and corresponding number of free parameters were 3302.6 (55), 3111.2 (83), 3103.3 (111), 3168.8 (139), respectively. The minimum BIC was found for the 4-class solution (see Table 3.2), suggesting that this is the preferred solution. The BLRT also found that the 4-class solution provided a significant improvement relative to the 3-class solution. Additionally, despite the BLRT for the 5-class solution showing that it provided a better fit than the 4-class solution, the best likelihood value was not replicated in 38 out of 49 bootstrap draws, making the *p*-value untrustworthy to a local maximum. Additionally, the small sample size of 114 individuals, along with 27 variables, requires the average number of individuals within a class to be equal to at least the number of variables used in the model (Nylund et al., 2007), making solutions more than four classes invalid. Based on the fit indices in Table 3.2 along with theoretical justification I adopted the 4-class solution.

[1] Other transformations such as inverse, square root and log did not normalise data.

Table 3.2 LCA fit statistics for 2-5 class models

Classes	LL	BIC	Adjusted BIC	AIC	Parameters	BLRT	Entropy
2	-1521.06	3302.61	3128.77	3152.12	55	964.15*	1
3	-1359.05	3111.20	2848.86	2884.10	83	324.02*	.98
4	**-1288.79**	**3103.29**	**2752.46**	**2799.57**	**111**	**140.52***	**.98**
5	-1255.23	3168.79	2729.46	2788.46	139	67.11*	.99

*p<.001; **Bold** text designates the best fitting model.
Note: LL, Log-likelihood value; BIC, Bayesian Information criteria; AIC, Akaike Information Criteria; BLRT, bootstrap likelihood ratio test.

3.4.2 Characteristics of the 4-class model

A visual plot of class probabilities is shown in Figure 3.1

Class 1 (n=36/114) accounted for 31.6% of the sample and demonstrated overall the lowest probabilities for all items. Class 1 will be referred to as 'control-LC'.

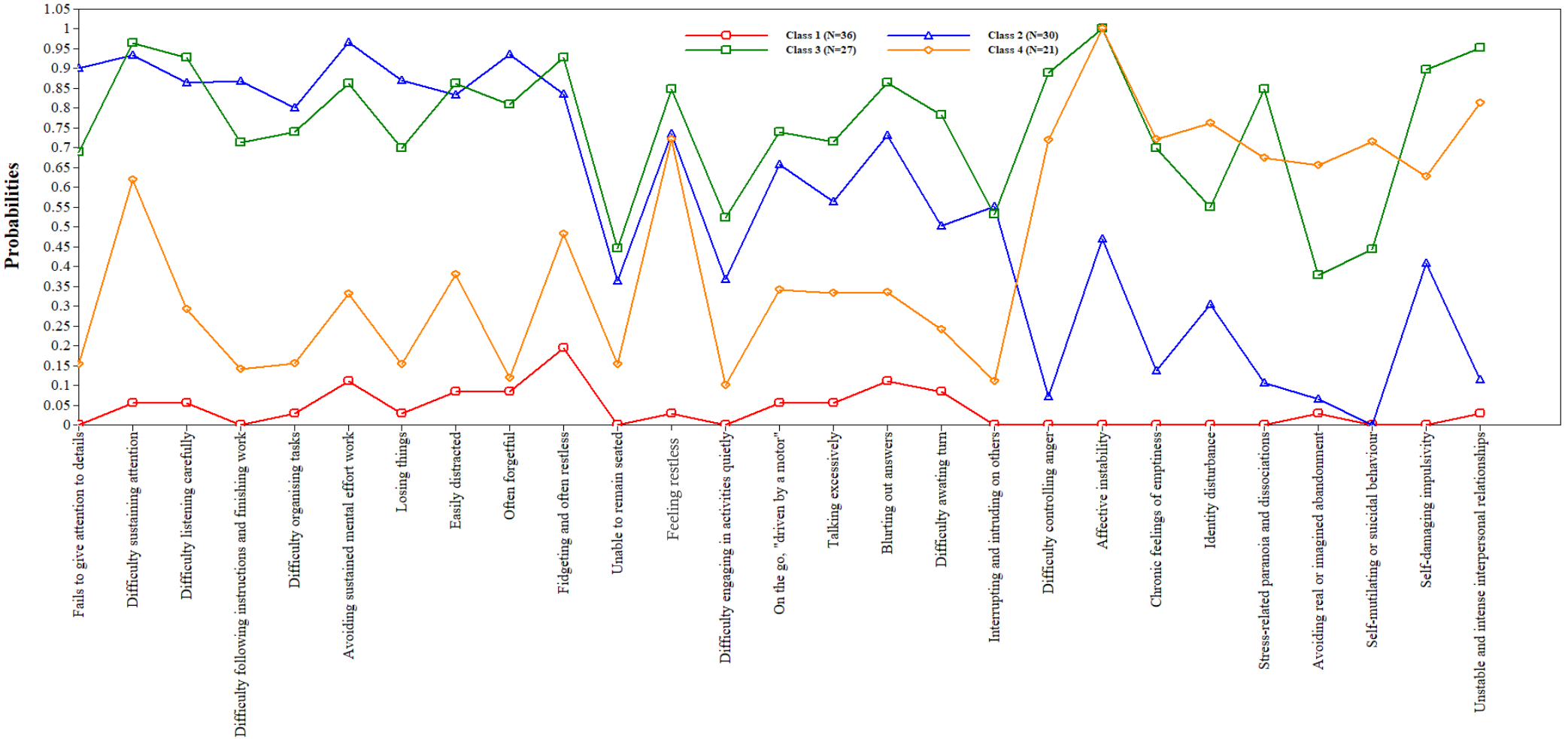
Class 2 (n=30/114) accounted for 26.3% of the sample and showed high probabilities for the inattentive symptoms of ADHD, intermediate to high probabilities for hyperactive/impulsive symptoms of ADHD, and very low probabilities for most BPD symptoms, except for two; "affective instability" (.47) and "self-damaging impulsivity" (.41). This class therefore reflects individuals with a diagnosis of ADHD, who also have a high probability of the two most commonly overlapping symptoms with BPD; affective instability and impulsivity. Note that although affective instability is not defined as a core symptom in the DSM-5 classification of ADHD, it is recognized as a characteristic feature that supports the diagnosis of ADHD (American Psychiatric Association, 2013). Class 2 will be referred to as 'ADHD-LC'.

Class 3 (n=27/114) accounted for 23.7% of the sample and showed intermediate to high probabilities for both ADHD and BPD symptoms. This class reflects individuals meeting diagnosis for both ADHD and BPD, originally identified as comorbid ADHD/BPD cases. Class 3 will be referred to as 'comorbid-LC'.

Lastly, class 4 (n=21/114) accounted for 18.4% of the sample and demonstrated high probabilities for BPD symptoms, low probabilities for inattentive symptoms of ADHD except for "difficulty sustaining attention" (.62), and low probabilities for hyperactive/impulsive symptoms of ADHD except for "feeling restless" (.72). Class

4 represents cases with a diagnosis of BPD, yet also having a high probability for overlapping symptoms of ADHD, such as sustained attention and feeling restless. Class 4 will be referred to as ‘BPD-LC’.

Figure 3.1 Latent class probabilities for adult symptoms of ADHD and BPD in female patients with a diagnosis of ADHD, BPD, or both



3.4.3 Class membership compared to DSM-5 diagnosis

The relationship between latent class memberships and DSM-5 diagnoses for the female sample in this study are summarised in Figure 3.2.

The individuals identified in the control-LC (n=36) correspond exactly to the same individuals identified in the control group, who did not meet criteria for a clinical diagnosis.

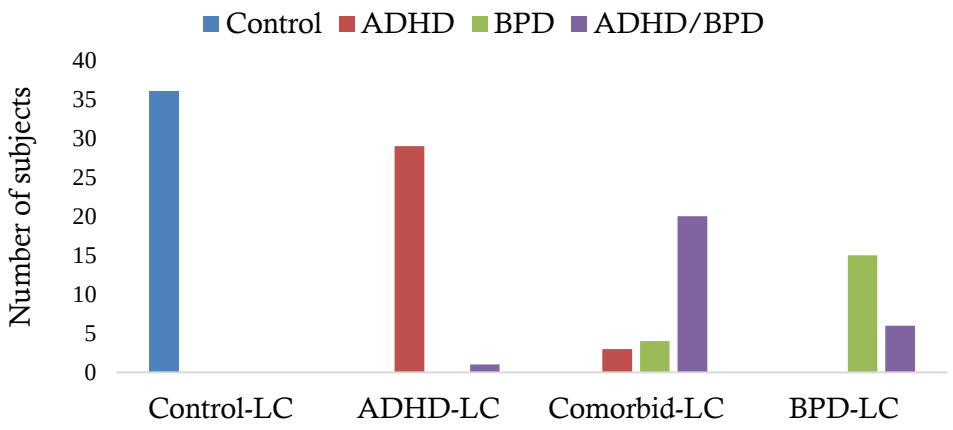
Patients diagnosed with DSM-5 ADHD only (n=32), were mostly categorised in the ADHD-LC (n=29), reflecting intermediate to high probabilities for ADHD symptoms and low probabilities for BPD symptoms. Three individuals with DSM-5 ADHD only were placed in the comorbid-LC. These three individuals had the following four symptoms of BPD marked as present; "inappropriate, intense anger or difficulty controlling anger", "affective instability", "self-damaging impulsivity" and "unstable and intense interpersonal relationships", making them sub-threshold cases for BPD based on the DSM-5 definition of the disorder.

Of the patients meeting DSM-5 criteria for BPD (n=19), 15 individuals were placed in the BPD-LC, marked primarily by high probabilities for BPD symptoms, and low probabilities for ADHD symptoms, with the exception of two items. The remaining four individuals were placed in the comorbid-LC, two of which reported less than three symptoms of ADHD in childhood, and therefore did not meet DSM-5 ADHD diagnostic criteria, which requires several symptoms before the age of 12 years, defined as three or more in this study (see section 2.3.3.1 in chapter 2 for more details). This could potentially reflect inaccurate retrospective recall, since the study had no prospective or informant data on childhood ADHD to clarify this point. One other patient could not provide information about her childhood[2] and was treated as having no childhood symptoms; and one other reported four adult symptoms in each domain of inattention and hyperactivity/impulsivity making her sub-threshold to the DSM-5 adult ADHD criteria of five or more in either domain.

[2] This patient could not provide any information for childhood symptoms. She met criteria for current/adult symptoms (more than five in the domains of inattention and hyperactivity/impulsivity), but DSM-5 also requires the presence of several childhood ADHD symptoms. She was therefore classified as a BPD case, without ADHD diagnosis.

Finally, of the 27 individuals who met DSM-5 criteria for both ADHD and BPD, 20 showed up in the comorbid-LC, as comorbid ADHD/BPD cases. Six participants were placed in BPD-LC, reflecting predominantly a BPD diagnosis. These individuals met DSM-5 criteria for both BPD and ADHD yet were placed in the BPD-LC. They all had five or less inattentive symptoms and more severe BPD symptoms, which could explain their belonging to the BPD-LC, reflecting predominantly a BPD diagnosis. In this study, individuals with a DSM-5 ADHD diagnosis, who were mostly placed in the ADHD-LC, had a greater number of inattentive symptoms and met criteria for the predominantly inattentive presentation of ADHD, with less severe hyperactivity/impulsivity symptoms.

Figure 3.1 Distribution of DSM-5 diagnostic categories across latent classes (LC)



3.4.4 Characteristics of DSM-5 diagnostic groups and the adult latent classes

In the following sections comparing the diagnostic and LCA groups across a range of measures, there were similar findings for both the DSM-5 and LCA classifications. Given that the latent classes mapped onto well to the DSM-5 classifications, the findings are presented first for the DSM-5 classification, and then any differences with the LCA classification are indicated. The characteristics of the sample on various outcome measures are in Table 3.3 and Table 3.4.

Age and IQ:

The DSM groups significantly differed in age, $X^2(3) = 9.2$, $p=.027$ (Mean in years (SD): control=29.44 (8.29); ADHD=36.94 (11.54); BPD=35.37 (11.39); ADHD/BPD=32.81(13.18) and IQ, F (3,109) = 7.07, $p<.001$ (Mean (SD): control=108.86(9.84); ADHD= 106.03(13.51); BPD= 97.05(13.82); ADHD/BPD= 96.73(12.71).

The latent classes were matched on age $X^2(3) = 7.75$, $p=.051$, but also differed in IQ, F (3, 109) = 9.67, $p<.001$ (Mean (SD): control-LC=108.86(9.84); ADHD-LC= 106.13(13.89); BPD-LC= 102.43(11.53); comorbid-LC= 92.96(12.56).

3.4.4.1 ADHD and BPD symptom severity

DSM-5 classification:

Significant group differences were present for current ADHD symptoms ($X^2(3) = 85.3$, $p<.001$). Post-hoc analyses indicated that all three clinical groups had significantly more current ADHD symptoms than the control group ($p<.05$). Additionally, the ADHD and comorbid ADHD/BPD groups had significantly higher ADHD symptoms than the BPD group ($p<.05$), whereas no significant differences were seen between the ADHD and comorbid ADHD/BPD groups ($p=1$). After adjustment for multiple testing ($p=.004$), differences between the control group and the BPD group, as well as comorbid ADHD/BPD and BPD groups were no longer significant.

Ratings on the ZAN-BPD showed significant group differences, $X^2(3) = 96.52$, $p<.001$. All three clinical groups had elevated borderline personality symptoms compared to controls ($p\leq.001$). The ADHD group had significantly lower ($p\leq.001$) borderline personality symptoms compared to both the BPD and comorbid ADHD/BPD groups, who showed no differences between each other on the measure ($p=1$). All comparisons remained robust to Bonferroni correction (adjusted $p=.004$).

LCA classification:

Results were similar using the LCA classifications. For current ADHD symptoms, in addition to the parallel results found with the DSM diagnostic groups, a Bonferroni adjusted significant difference was also found between comorbid-LC and BPD-LC (p<.001). Regarding borderline symptomatology, the results of the latent classes matched the DSM group comparisons.

3.4.4.2 Emotional dysregulation

DSM-5 classification:

Significant group differences were detected for the ALS-SF ($X^2(3) = 65.66$, p<.001), WRAADDS-EDS ($X^2(3) = 79.99$, p<.001) and ARI ($X^2(3) = 60.27$, p<.001). All three clinical groups reported significantly elevated levels of emotional dysregulation on all measures compared to controls (p<.001), and these significant differences were robust to the adjusted p=.004. Additionally, no differences were detected between the ADHD and BPD groups, as well as the BPD and comorbid ADHD/BPD groups on all three measures (p>.05). The ADHD group reported significantly lower levels of emotional dysregulation on all three scales compared to the comorbid ADHD/BPD group (p<.05), which was not robust to the Bonferroni adjusted p=.004.

LCA classification:

Regarding case-control differences, the latent classes displayed an equivalent picture compared to the DSM-5 diagnostic groups on all three measures. Differences between clinical latent classes also matched to the DSM group comparisons. Regarding the ARI and WRAADDS-EDS, in addition to the matching results obtained from DSM group comparisons, after Bonferroni correction for multiple testing (adjusted p=.004), the difference between ADHD-LC and comorbid-LC remained significant (p≤.001).

3.4.4.3 Co-occurring depression and anxiety

DSM-5 classification:

There were significant group differences on depression, $X^2(3) = 75.90$, $p<.001$ and anxiety, $X^2(3) = 79.96$, $p<.001$. Post-hoc tests showed elevated self-reported depression and anxiety in the clinical groups compared to controls ($p<.05$). Additionally, the ADHD group showed less anxiety and depression compared to both BPD and comorbid ADHD/BPD groups, yet no differences were seen between the BPD and comorbid ADHD/BPD groups. Except for the depression subscale between the control and ADHD groups, and the anxiety subscale between the ADHD and BPD groups, comparisons were robust to the Bonferroni adjusted $p=.004$.

LCA-classification:

Regarding latent classes, all comparisons were analogous to the DSM group comparisons, except for the anxiety subscale between the ADHD and BPD groups not showing any significant differences.

3.4.4.4 Childhood trauma

DSM-5 classification:

Ratings on different domains of childhood maltreatment showed significant group differences for physical abuse, $X^2(3) = 25.97$, $p<.001$, emotional neglect, $X^2(3) = 35.03$, $p<.001$, emotional abuse, $X^2(3) = 44.59$, $p<.001$, physical neglect, $X^2(3) = 36.49$, $p<.001$ and sexual abuse, $X^2(3) = 27.45$, $p<.001$. The control group reported significantly less emotional abuse than the ADHD group ($p=.004$), which was robust to Bonferroni adjustment ($p=.004$). Differences between the control and ADHD groups on all other subscales of childhood maltreatment were non-significant. Both BPD and comorbid ADHD/BPD groups significantly differed from controls, reporting more severe childhood trauma in all five domains, and all differences were robust to the Bonferroni corrected $p=.004$.

Regarding comparisons in the clinical groups, there were no differences in any domain of childhood trauma between the BPD and comorbid ADHD/BPD groups (p=1). The ADHD and BPD groups only differed in the domain of physical neglect (p=.036), with the latter reporting more severe physical neglect, but this difference was not robust to the Bonferroni corrected p=.004. Finally, the ADHD and comorbid ADHD/BPD groups were significantly different in all domains of childhood trauma, apart from physical abuse, but differences were robust to Bonferroni correction, only in the domains of physical neglect and sexual abuse (p<.004).

LCA-classification:

Regarding the latent classes, the comparisons between the control-LC and the other latent classes reflecting a clinical diagnosis all displayed a similar picture compared to the case-control differences found in the DSM group comparisons. There were some differences between the ADHD-LC and comorbid-LC, as well as between ADHD-LC and BPD-LC, yet none were robust to Bonferroni correction.

3.4.4.5 Mind wandering

The DSM groups significantly differed on the MEWS, $X^2(3) = 69.30$, p<.001. Post-hoc tests revealed that all three clinical groups reported more frequent mind wandering than the control group *(*p<.001) but were not significantly different from one another.

An equivalent picture was displayed by the latent class.

3.4.4.6 Functional impairment

DSM-5 classification:

Ratings in different domains of impairment showed significant group differences for family, $X^2(3) = 49.95$, p<.001, social function, $X^2(3) = 70.25$, p<.001, life skills, $X^2(3) = 66.92$, p<.001, self-concept, $X^2(3) = 74.48$, p<.001, and risk-taking behaviours $X^2(3) = 32.39$, p<.001. The clinical groups reported significantly elevated impairment on all five subscales of the WFIRS-S (family, social function,

life skills, self-concept, risk-taking behaviour) compared to the control group (p<.05). With the exception of the risk-taking behaviour subscale between the control and BPD groups (p=.006), all differences were robust to the Bonferroni corrected p=.004. There were no significant differences between the BPD and ADHD groups, as well as the BPD and comorbid ADHD/BPD groups (p>.05) in all five domains of functional impairment. The ADHD group showed significantly less impairment in the domains of family and self-concept, with the latter only being robust to Bonferroni correction.

LCA classification:

Regarding case-control differences, a similar picture to the DSM group comparisons was displayed by the latent classes. Regarding comparisons between clinical latent classes, in addition to the non-significant differences between BPD-LC and ADHD-LC, as well as BPD-LC and comorbid-LC which was also comparable to the DSM group comparisons, the ADHD-LC reported significantly less impairment in the domains of family (p=.008), social (p=.005) and self-concept (p=.005), none of which were robust to Bonferroni correction (p=.004).

Table 3.3 Comparison of DSM-5 groups on measures of psychopathology

	Mean (SD)				Pairwise comparisons- Adjusted *p*					
	Control	ADHD	BPD	ADHD/BPD	Control vs ADHD	Control vs BPD	Control vs ADHD/BPD	ADHD vs BPD	ADHD vs ADHD/BPD	BPD vs ADHD/BPD
DIVA	.97 (1.2)	13.34 (2.6)	5.53 (4.0)	12.41 (3.0)	**<.001**	.020	**<.001**	**<.001**	1	.005
ZAN-BPD	.64 (1.3)	6.50 (3.9)	20.63 (4.26)	23.33 (5.9)	**.001**	**<.001**	**<.001**	**.001**	**<.001**	1
ARI	.97 (1.8)	5.16 (4.1)	7.68 (3.8)	9.07 (3.6)	**<.001**	**<.001**	**<.001**	.382	.015	1
WRAADDS-EDS	2.83 (2.5)	12.88 (3.8)	14.95 (2.6)	16.93 (2.8)	**<.001**	**<.001**	**<.001**	1	.017	.912
ALS-SF	7.03 (7.0)	28.84 (13.3)	33.84 (10.4)	38.52 (9.9)	**<.001**	**<.001**	**<.001**	.451	.012	.430
BSI_Depression	1.58 (2.1)	5.22 (4.6)	14.00 (6.3)	16.33 (5.5)	.022	**<.001**	**<.001**	**.001**	**<.001**	1
BSI_ Anxiety	1.31 (1.6)	7.06 (4.2)	12.68 (4.8)	15.41 (5.1)	**<.001**	**<.001**	**<.001**	.045	**<.001**	1
MEWS	6.36 (4.7)	32.97 (8.2)	29.95 (9.2)	33.00 (9.3)	**<.001**	**<.001**	**<.001**	1	1	1
WFIRS_family	2.17 (2.0)	7.06 (5.2)	10.00 (6.4)	12.50 (5.1)	**.001**	**<.001**	**<.001**	.951	.016	1
WFIRS_social	.86 (1.0)	7.87 (4.7)	13.47 (8.0)	14.22 (6.3)	**<.001**	**<.001**	**<.001**	.518	.065	1
WFIRS_life skills	3.06 (3.5)	16.94 (5.3)	15.89 (8.9)	21.15 (8.5)	**<.001**	**<.001**	**<.001**	1	1	.508
WFIRS_self concept	2.42 (2.0)	8.77 (4.2)	12.00 (2.6)	13.33 (2.1)	**<.001**	**<.001**	**<.001**	.161	**.002**	1
WFIRS_risk	1.91 (2.5)	6.16 (5.0)	6.74 (6.3)	9.23 (6.3)	**.001**	.006	**<.001**	1	.696	.807
	Mean ranks				**Pairwise comparisons- Adjusted *p***					
CTQ_physical abuse	40.21	56.19	70.79	72.76	.115	**.001**	**<.001**	.435	.143	1
CTQ_emotional neglect	35.36	55.41	72.58	78.79	.051	**<.001**	**<.001**	.352	.025	1
CTQ_emotional abuse	31.90	57.78	70.92	81.85	**.004**	**<.001**	**<.001**	.865	.018	1
CTQ_physical neglect	38.15	50.72	74.76	79.19	.521	**<.001**	**<.001**	.036	**.002**	1
CTQ_sexual abuse	44.47	50.69	69.87	74.24	1	**.003**	**<.001**	.062	**.003**	1

Note: *p* values in **bold** show significance after Bonferroni correction for 13 comparisons (adjusted *p*=.004).
DIVA, Diagnostic Interview for ADHD in Adults; ZAN-BPD, Zanarini rating scale for Borderline Personality Disorder; ARI, Affective Reactivity Index; WRAADDS-EDS, Wender-Reimher Adult Attention Deficit Disorder Scale- Emotional dysregulation subscale; BSI, Brief Symptom Inventory; CTQ, Childhood Trauma Questionnaire; MEWS, Mind Excessively Wandering Scale; WFIRS, Weiss Functional Impairment Rating Scale; ALS-SF, Affective Lability Scale- Short Form.

Table 3.4 Comparison of latent classes on measures of psychopathology

	Mean (SD)				**Pairwise comparisons- Adjusted *p***					
	Class 1	Class 2	Class 3	Class 4	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
DIVA	.97 (1.2)	13.23 (2.6)	13.41 (2.6)	5.14 (2.6)	**<.001**	**<.001**	.036	1	**<.001**	**<.001**
ZAN-BPD	.64 (1.3)	6.37 (4.4)	22.11 (6.4)	21.05 (4.9)	**.002**	**<.001**	**<.001**	**<.001**	**<.001**	1
ARI	.97 (1.8)	4.43 (3.8)	9.78 (3.0)	7.57 (3.8)	**.002**	**<.001**	**<.001**	**<.001**	.125	.953
WRAADDS-EDS	2.83 (2.5)	12.47 (3.6)	17.48 (2.2)	14.62 (2.8)	**<.001**	**<.001**	**<.001**	**.001**	1	.221
ALS-SF	7.03 (7.0)	28.13 (13.5)	37.67 (9.8)	35.48 (10.4)	**<.001**	**<.001**	**<.001**	.017	.140	.880
BSI_Depression	1.58 (2.1)	5.67 (4.7)	14.89 (6.9)	14.38 (6.1)	.011	**<.001**	**<.001**	**.001**	**.002**	1
BSI_ Anxiety	1.31 (1.6)	7.23 (4.3)	15.56 (5.3)	11.71 (4.7)	**<.001**	**<.001**	**<.001**	**<.001**	.155	.809
MEWS	6.36 (4.7)	33.30 (8.4)	34.74 (6.9)	27.52 (10.2)	**<.001**	**<.001**	**<.001**	1	.568	.289
WFIRS_family	2.17 (2.0)	7.00 (4.9)	13.07 (5.9)	8.90 (5.2)	**.002**	**<.001**	**<.001**	.008	1	.396
WFIRS_social	.86 (1.0)	7.10 (3.9)	15.81 (6.8)	11.95 (6.4)	**<.001**	**<.001**	**<.001**	.005	.592	.882
WFIRS_life skills	3.06 (3.5)	17.41 (5.2)	21.41 (8.3)	15.00 (8.6)	**<.001**	**<.001**	**<.001**	1	1	.184
WFIRS_self concept	2.42 (2.0)	8.83 (4.2)	12.96 (2.8)	12.10 (2.4)	**<.001**	**<.001**	**<.001**	.005	.131	1
WFIRS_risk	1.91 (2.5)	5.45 (4.5)	10.58 (6.5)	6.00 (5.4)	**.003**	**<.001**	.012	.056	1	.087
	Mean ranks				**Pairwise comparisons- Adjusted *p***					
CTQ_physical abuse	40.21	56.47	69.70	72.93	.115	**<.001**	**<.001**	.453	.236	1
CTQ_emotional neglect	35.36	55.13	77.61	74.40	.093	**<.001**	**<.001**	.029	.139	1
CTQ_emotional abuse	31.90	57.77	75.44	76.64	.005	**<.001**	**<.001**	.140	.196	1
CTQ_physical neglect	38.15	51.27	76.20	75.52	.475	**<.001**	**<.001**	.011	.029	1
CTQ_sexual abuse	44.47	51.88	69.35	72.62	1	**.001**	**<.001**	.064	.028	1

Note: *p* values in **bold** show significance after Bonferroni correction for 13 comparisons (adjusted p=.004).
Class1= control-CL, Class 2= ADHD-CL, Class 3=comorbid-CL, Class 4=BPD-CL
DIVA, Diagnostic Interview for ADHD in Adults; ZAN-BPD, Zanarini rating scale for Borderline Personality Disorder; ARI, Affective Reactivity Index; WRAADDS-EDS, Wender-Reimher Adult Attention Deficit Disorder Scale- Emotional dysregulation subscale; BSI, Brief Symptom Inventory; CTQ, Childhood Trauma Questionnaire; MEWS, Mind Excessively Wandering Scale; WFIRS, Weiss Functional Impairment Rating Scale; ALS-SF, Affective Lability Scale- Short Form.

3.5 Discussion

This study investigated the phenotypic overlap between ADHD and BPD. The main aim was to explore the similarities and differences between female patients with ADHD, BPD, comorbid ADHD/BPD and healthy controls on various measures of psychopathology. The DSM-5 approach to classification for both ADHD and BPD relies on symptom count thresholds, which are to some extent arbitrary, given that both disorders reflect impairing extremes of dimensional traits (Chen et al., 2008; Clark, 2007). Therefore, LCA was undertaken as an empirical approach to classification, and results were compared using both DSM-5 and LCA defined clinical groups.

The LCA and DSM-5 diagnostic classification groups cross-validated well. Despite the overlap of certain symptoms in ADHD and BPD, the DSM-5 criteria, that relies on clusters of symptoms by applying symptom count thresholds, appears to be specific enough to delineate the disorders from one another in a similar way to the more empirical approach using LCA, indicating the validity of the constructs used.

Regarding the LCA, the results indicated that the four-class solution best fits the data, which was identical to the number of groups participants were classified in by using predefined DSM-5 criteria. Furthermore, the number of individuals classified in each latent class was similar to the number of individuals in the pre-defined DSM groups, with only very few cross-over of cases.

Regarding the characteristics of the sample, overall the results indicated that the empirical and DSM-5 diagnostic approaches gave comparable results. One class (control-LC) had the lowest probability for all clinical symptoms, thus referring to the healthy control group. The other three classes all had a mixture of ADHD and BPD symptoms with varying probabilities. One class (ADHD-LC) had predominantly symptoms of inattentive ADHD, with less severe symptoms of hyperactivity/impulsivity, and a very low occurrence of BPD symptoms, except for affective instability (criterion 6 of BPD) and impulsivity (criterion 2 of BPD). One class (comorbid-LC) had symptoms of the combined type of ADHD together with symptoms of BPD. And the last class (BPD-LC) had a high BPD symptoms

probability combined with symptoms of inattention and hyperactivity/impulsivity to different degrees. In fact, symptoms of BPD were not found to occur without at least some ADHD symptomatology, and vice versa.

These findings are not in line with the only other latent class study results of ADHD and BPD females, where the model resulted in one class of patients with a primary diagnosis of ADHD and no symptoms of BPD (van Dijk et al., 2011). Some significant methodological differences could explain the discrepancies. In the current study, comorbid axis I or II disorders were excluded to associate significant findings to ADHD or BPD, rather than other co-occurring conditions. Comorbidities, other than schizophrenia, were not excluded in van Dijk et al.'s study, in addition to having a bigger clinical sample size of 103 patients compared to 78 in the current study.

When examining further the symptom probabilities of the latent classes, it appeared that all three LCA classes reflecting a clinical diagnosis could not be easily distinguished on the amount of ADHD symptoms. Specifically, hyperactivity/impulsivity symptoms had higher probabilities than inattentive symptoms in the BPD-LC, indicating the relative lack of specificity and broad formulation of the hyperactivity/impulsivity criteria in the DSM-5 (e.g. "fidgeting and often restless", "feeling restless"). These hyperactivity/impulsivity symptoms were found to be less specific to the latent classes compared to symptoms of BPD, which had much lower probabilities in the ADHD-LC, with the exception of "affective instability and "impulsivity" (both commonly associated features of ADHD).

The fact that the three LCA classes incorporating the clinical cases had symptoms of both diagnoses to varying degrees, illustrates the heterogenous profile of ADHD and BPD, and their comorbid and overlapping picture (Philipsen, 2006; Philipsen et al., 2009).

Regarding the rating scale and interview measures, increased levels of emotional dysregulation, depression and anxiety, mind wandering, functional impairment, and current ADHD and BPD symptoms were seen in all three clinical groups compared to controls, whether defined using DSM-5 or LCA.

Regarding childhood maltreatment, the BPD and comorbid ADHD/BPD groups reported significantly more severe childhood abuse and neglect compared to controls, but non-significant differences compared to the ADHD group. However, no differences were seen between the ADHD and control groups. This is explained by the fact that mean ranks of the childhood trauma subscales for the ADHD group were intermediate between the control and BPD groups. To explain these differences further, a larger sample is required to clarify whether CTQ scores for the ADHD group are similar to the BPD group, the control group, or are indeed intermediate with differences from both controls and BPD.

A key aim of this thesis was to investigate cross-disorder similarities and differences between patients meeting clinical criteria for ADHD and BPD. By taking an exploratory approach, I hypothesised that some symptoms such as emotional dysregulation or mind wandering might show differences across the disorders; for example, with higher levels of mind wandering in ADHD than BPD. However, the results presented in this chapter using rating scale measures of psychopathology show either no difference or only subtle differences between the disorders across a wide range of measures. In particular, retrospective self-report measures of mind wandering *and* emotional dysregulation were not able to distinguish the two clinical disorders, *with* elevated ratings seen in both. These two findings provide a basis for *a more detailed* investigation using experience sampling method in chapters four and *five of this* thesis.

Regarding childhood trauma, this study suggests that trauma is not only related to BPD (Golier et al., 2003; Zanarini & Frankenburg, 1997), but also to ADHD, as previously reported (Ferrer et al., 2017). There were no significant differences between the disorders on all subscales of the CTQ. Although, as discussed above, small differences in exposure to trauma may emerge in larger datasets, these may be relatively subtle and insufficient to discriminate one condition from the other. This is important since some are unlikely to make a diagnosis of ADHD in people who give an account of childhood maltreatment, potentially compromising the targeting of appropriate treatments (Ferrer et al., 2017). Whereas experiencing childhood

traumas is associated with later development of more general psychopathology (Teicher & Samson, 2013), to date, there is no data to suggest that a history of childhood trauma moderates the effects of medications on ADHD; and the findings reported here do not find a clear distinction in reporting of childhood trauma in ADHD and BPD. Future studies are needed to explore the moderating role of childhood maltreatment in the treatment of ADHD.

As expected, current ADHD symptoms measured by the DIVA interview were significantly elevated in the ADHD groups compared to the BPD groups. Similarly, current symptoms of BPD were significantly elevated in the BPD groups compared to the ADHD groups. Despite these groups not being different on several measures of psychopathology as discussed above, the clinical interviews designed to identify and diagnose patients with each of the disorders seem to discriminate well between ADHD and BPD. One reason for this could be that each of the disorders have more unique and specific symptoms than overlapping ones. In fact, symptoms such as chronic feelings of emptiness, dissociation and identity disturbances, problems with abandonment, and self-mutilating or suicidal behaviour, which are all core symptoms of DSM-5 BPD diagnosis, had high probabilities in the BPD-only class, and much lower probabilities in the ADHD-only class.

This study therefore supports the view that individual symptoms and associated factors (such as emotional dysregulation, mind wandering, anxiety, childhood maltreatment and impairments in various domains of everyday life) are non-specific measures that are seen across both disorders and cannot be relied upon to discriminate ADHD from BPD. On the other hand, self-reported depression, although significantly elevated in both ADHD and BPD groups compared to controls, was significantly higher in the BPD groups than the ADHD groups. In this study, 79% of the BPD group were on concomitant anti-depressants, compared to a much lower rate of 19% in the ADHD group, which could be explained by the higher levels of depressive symptoms in the BPD group.

Regarding symptoms of emotional dysregulation, these are considered to be a characteristic feature of ADHD that supports the diagnosis according to the DSM-5, yet they are a core criterion of BPD (American Psychiatric Association, 2013). Nonetheless, the data provided here, and previous research suggests that emotional

dysregulation may be as much a part of ADHD as the core symptoms of inattention and hyperactivity/impulsivity (Barkley & Fischer, 2010; Skirrow et al., 2014). The reason for excluding this from the DSM-5 ADHD diagnostic criteria reflects the fact that emotional dysregulation is seen in many different mental health disorders and is not good at discriminating one condition from another. Related to this, the classification systems are designed to provide an optimal algorithm for use by health care professionals to separate one condition from another, yet some symptoms reflect dimensions of psychopathology and are often seen across various mental health conditions. This was shown in the LCA results by the presence of 'affective instability' and 'impulsivity' in the ADHD-LC, which are specific diagnostic criteria of BPD; as well as the presence of some core symptoms of ADHD, 'fidgeting and often restless' and 'feeling restless', in the BPD-LC. Despite the DSM criteria working well to classify patients with ADHD and BPD, in comorbid ADHD/BPD cases it is unclear how transdiagnostic symptoms, such as affective instability, are related to the two conditions, and what to expect from specific treatments. For example, stimulants may reduce emotional instability in some comorbid cases and not others, depending on the origin of emotional instability. More detailed investigations are needed to evaluate whether there are qualitatively distinct types of emotional instability related to ADHD and BPD, or whether these are indistinguishable. Related to this question, are there stimulant responsive and non-responsive types of emotional dysregulation depending on the origins of the symptoms? Further work is required to clarify these points.

In general, the comorbid ADHD/BPD groups seemed to be more similar to the BPD group than the ADHD group, particularly for anxious and depressive symptoms, but not for mind wandering, in which they were more similar to the ADHD group.

Overall, these findings illustrate the considerable overlap of ADHD and BPD but should be considered in light of some limitations. First, the generalisability of the results is limited by the specific patient sample I recruited for this study. The study had strict inclusion criteria (see section 2.3.1 in chapter 2), and specifically excluded individuals on antipsychotics and mood stabilisers. Yet, a national audit of prescribing for patients with personality disorders in England showed that one in

five patients are being prescribed mood stabilisers (POMH, 2014). This sample might therefore have less severe mood and other symptoms than the majority of BPD patients seen in clinical settings. Moreover, the results cannot be generalised to males, as the sample consisted of only females. Given that it is mostly women who receive therapy for BPD while the sex ratio for adult patients with ADHD is more equally divided, the results of this study are more representative for the clinical population with BPD than those with ADHD. However, an advantage of this approach is that sex differences are not included as a confounder, and most studies of ADHD focus on male only samples or samples with a higher proportion of males to females. It is therefore valuable to the understanding of ADHD to investigate female only samples.

Second, this study employed a retrospective design in identifying onset of symptoms during childhood or adolescence, which is susceptible to recall bias. There was no information from informants when making a diagnosis based on the DSM-5 definitions of the disorders, although the accuracy of retrospective informant reports has also been questioned (Olino & Klein, 2015). The recall bias is particularly an issue in the DIVA (Kooij, 2013) interview, where symptoms of childhood ADHD are assessed retrospectively, and several participants disclosed having little or no memory of their childhood experiences. Thus, it was decided to exclude childhood symptoms from the LCA.

Despite these limitations, which should be addressed in future research, several clinical implications arise from the findings reported here. A first implication is that in cases of a diagnosis of BPD or ADHD, the other condition should always be considered. Both disorders are considered to reflect the extreme and impairing end of a dimensional trait, and symptoms commonly may also occur at sub-diagnostic levels (Chen et al., 2008; Clark, 2007). Therefore, it is expected that patients with BPD display some ADHD traits as part of a normal population distribution, and patients with ADHD may display some traits of BPD.

A second implication is that ADHD and BPD cannot be easily differentiated on the basis of individual symptoms and impairments, particularly those that overlap both disorders. A key point is that the full DSM-5 criteria for ADHD and BPD, using clusters of symptoms to define clinical syndromes, appears to work well in

classifying ADHD and BPD as separate disorders. However, given the state of knowledge, treatments for both disorders in comorbid cases should be considered at the same time. Further research is needed to better understand the effects of treatments in the comorbid group.

Chapter 4: Wandering minds in ADHD and BPD

4.1 Abstract

Attention-deficit/hyperactivity Disorder (ADHD) and borderline personality disorder (BPD) have overlapping symptoms that make differential diagnosis challenging. We previously proposed that excessive spontaneous mind wandering (MW) reflects a measurable component of psychopathology that might distinguish ADHD from other psychiatric conditions.

Using a questionnaire measure of excessive MW and a more objective experience sampling method, we investigated different aspects of MW in daily life, in 28 ADHD, 19 BPD, 22 comorbid ADHD/BPD, and 29 control female participants.

The ADHD, BPD and comorbid ADHD/BPD groups all reported heightened frequency and intensity of MW compared to controls. However, no differences were found between the clinical diagnoses. When depression and anxiety were controlled for, significant differences only persisted between controls and ADHD, who also showed significantly elevated intensity of MW compared to BPD and comorbid ADHD/BPD. We found no MW instability differences amongst clinical cases as well as cases versus controls. Negative content of MW was higher in BPD and comorbid ADHD/BPD compared to controls, whereas no differences appeared between ADHD and controls. When controlling for depression and anxiety, the differences between BPD and comorbid ADHD/BPD and controls dissipated.

Excessive spontaneous MW was found to be a transdiagnostic process present in both ADHD and BPD. Yet, the underlying mechanisms of this subjective experience may be driven by different processes. The association of anxiety and depression with MW in BPD but not ADHD should be further explored in the context of understanding the heterogeneity of excessive spontaneous MW.

4.2 Introduction

Disentangling the similarities and differences between attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) is a question that frequently arises in clinical practice (Moukhtarian, Mintah, Moran, & Asherson, 2018; Xenaki & Pehlivanidis, 2015). High comorbidity of around 20% between the

disorders (Ferrer et al., 2010) and overlap of key clinical features (Matthies & Philipsen, 2014; Philipsen, 2006), has led to questions around the distinction between ADHD and BPD (Xenaki & Pehlivanidis, 2015). Importantly, current evidence on treatments diverge, since drug treatments in the form of stimulants or atomoxetine are effective in the treatment of ADHD (Castells et al., 2011; Cunill, Castells, Tobias, & Capellà, 2013), whereas to date, drug treatments for BPD have yet to demonstrate evidence of effectiveness, making this an important ongoing area of clinical enquiry (NICE, 2009).

Although the diagnosis of ADHD relies on the presence of impairing levels of inattention and/or hyperactivity/impulsivity, associated features of ADHD show considerable overlap with the symptoms used to define BPD (Philipsen, 2006; Philipsen et al., 2009). Emotional dysregulation, poor impulse control and unstable interpersonal relationships are core features of BPD which are commonly seen in individuals with ADHD (Asherson et al., 2014; Moukhtarian et al., 2018; Philipsen, 2006). These common features can hamper the differential diagnosis process and represent a significant risk of misdiagnosis, leading to individuals not receiving optimal treatments for their clinical condition (Asherson et al., 2014).

One approach to this problem is to focus on aspects of psychopathology that might distinguish ADHD and BPD. Regarding ADHD, we previously found that excessive spontaneous mind wandering (MW) is strongly associated with ADHD, and proposed that this form of MW reflects a measurable component of psychopathology that might distinguish ADHD from other psychiatric conditions (Bozhilova, Michelini, Kuntsi, & Asherson, 2018; Mowlem et al., 2016).

MW is a universal phenomenon that takes up around 50% of daily thinking time (Smallwood & Schooler, 2015) and occurs when one's mind drifts away from the primary task on-hand and focuses on internal, task-unrelated thoughts and images (Smallwood, McSpadden, & Schooler, 2007). Although not all forms of MW reflect pathological processes (Seli, Smallwood, Cheyne, & Smilek, 2015), excessive spontaneous MW, that is detrimental to performance, has been proposed as a possible mechanism underlying many of the symptoms and impairments of ADHD (Mowlem et al., 2016). However, excessive spontaneous MW is also known to be

associated with other disorders such as anxiety and depression, and may therefore reflect a heterogenous transdiagnostic mental phenomena (Christoff, Irving, Fox, Spreng, & Andrews-Hanna, 2016; Hoffmann, Banzhaf, Kanske, Bermpohl, & Singer, 2016; Ottaviani & Couyoumdjian, 2013; Xu, Purdon, Seli, & Smilek, 2017).

The first study of MW in ADHD found that the frequency of task-unrelated thoughts was higher in college students with a childhood history of ADHD compared to controls, using an experience sampling method (ESM) during a sustained-attention task (Shaw & Giambra, 1993). Spontaneous MW measured, was also found to be higher in students with ADHD compared to controls, and correlated with ADHD symptom severity, using a self-report scale of spontaneous MW (Seli et al., 2015). In an adult community sample, ADHD symptoms were positively correlated with frequency of, and lack of awareness of MW, using both laboratory and daily-life ESM measures (Franklin et al., 2014). Moreover, awareness of MW partially mediated the relationship between ADHD symptoms and the detrimental impact of MW, suggesting that increasing awareness of MW in ADHD might lead to functional improvements (Franklin et al., 2014).

Recently, our group found significantly elevated ratings of MW in ADHD participants compared to controls in two independent adult samples, using a measure of excessive spontaneous MW: the Mind Excessively Wandering Scale (MEWS) (Mowlem et al., 2016). The MEWS is a 15-item self-rated scale, designed to capture the subjective accounts of MW by individuals with ADHD: thoughts constantly on the go, thoughts that jump and flit from one topic to another, and multiple thoughts at the same time. MEWS scores showed high sensitivity (~0.9) and specificity (~0.9) for discriminating between ADHD cases and controls and accounted for unique variance in self-reported functional impairments. In one sample MEWS scores carried the most importance in the model (β=.49), followed by inattention (β=.29) and hyperactivity/impulsivity (β=.17), indicating the clinical relevance of MW in ADHD to impairment in daily-life (Mowlem et al., 2016).

Taken together, these findings shed light on the significant association between ADHD and MW, suggesting that measures of MW might have utility in the diagnostic process. Although these findings confirm sensitivity of MW measures to

ADHD, they do not investigate specificity compared to other common psychiatric disorders. For example, it is already established that higher levels of MW are associated with depression (Hoffmann et al., 2016), and this could be the case for other disorders. Nevertheless, we hypothesise that MW in ADHD may have distinctive characteristics compared to MW in other disorders, such as depressive ruminations, anxious worrying and obsessional thoughts.

Regarding BPD, we identified only two investigations of MW (Kanske et al., 2016; Scheibner, Spengler, Kanske, Roepke, & Bermpohl, 2016). Using an ESM assessment of MW during a reaction time task no differences were found in the frequency of MW in BPD compared to controls, although BPD cases reported more negative thoughts and greater MW instability (Kanske et al., 2016). In contrast, another study reported a higher frequency with longer duration of MW in BPD cases compared to controls, using an experimenter-prompted mindfulness task (Scheibner et al., 2016). Based on these two studies, it is unclear whether there is greater frequency or instability of MW in BPD compared to controls.

Based on the findings to date, we do not know whether excessive MW is a clinical feature of BPD, or whether measures of MW can be used to distinguish ADHD from BPD. We therefore set out to investigate the frequency of MW in ADHD and BPD using two measurement approaches. First using the MEWS self-report scale of spontaneous MW, and secondly using ESM measures of MW in everyday life. Based on previous findings, we hypothesised that MW would have distinctive characteristics in ADHD from that seen in BPD. More specifically, that MW would be more heightened in ADHD than BPD, and that the content of MW would reflect higher negative valence thoughts in BPD than in ADHD.

4.3 Methods

4.3.1 Participants

98 female participants aged 18–65 years (M=33.4, SD=11.3) were recruited. Controls, not meeting criteria for ADHD or BPD, were recruited through advertisements in King's College London, volunteer databases, and within the local community. Clinical cases were recruited from ADHD and borderline personality

specialist clinics in the South and Midland regions of England. Members of the clinical care teams identified potentially eligible participants and referred them to the research team. Clinician diagnoses were based on DSM criteria for ADHD and BPD (American Psychiatric Association, 2013), and validated for research by members of the research team using the Diagnostic Interview for ADHD in Adults (DIVA) (Kooij, 2013) and the Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD) (Zanarini, 2003) to maintain reliability and consistency of diagnosis across the whole sample (see section 2.3.3.1 in chapter 2 for details on diagnostic measures). Co-morbidities were excluded using a checklist of common mental health conditions by screening clinical case records. Exclusion criteria for the clinical and control groups were: male gender; history of bipolar I and II, recurrent depressive episodes, and schizophrenia; current Axis I disorders; head injury or neurological conditions; IQ<70; and current treatment with psychoactive medication, specifically mood stabilisers and/or anti-psychotics (except concomitant medication for non-recurrent depression[1]). Participants on stimulant medication for ADHD were asked to come off this medication for 48 hours before the baseline assessment and the following five days during ESM. Due to the frequent drug and alcohol use in ADHD (Bernardi et al., 2012; Fayyad et al., 2007; Kessler et al., 2006) and BPD (Fyer, Frances, Sullivan, Hurt, & Clarkin, 1988; Zanarini et al., 1998) populations, we excluded individuals with addiction disorders, but not for elevated alcohol and drug use (see section A in supplementary 4 for details).

[1] n=31 clinical cases were on concomitant anti-depressants, which constitutes around 45% of the clinical sample. To run sensitivity analyses without these cases, our clinical sample size would greatly decrease (ADHD= 20, BPD=4, ADHD/BPD= 14), making between group comparisons unmeaningful.

4.3.2 Materials and procedure

4.3.2.1 Symptom measures

Self-reported excessive MW was assessed using the MEWS. The MEWS is a self-rated scale measuring severity of excessive mind wandering. It consists of 15 items rated on a 4-point Likert-scale (0=not at all to 3=nearly all the time or constantly) (Mowlem et al., 2016).

Comorbid depression and anxiety was measured by the Brief Symptom Inventory (BSI) (Derogatis, 1993). The BSI is a self-rated measure consisting of 53-items evaluating psychological distress and psychiatric disorders in nine domains including depression and anxiety on a 4-point Likert-scale (0=not at all to 3=extremely).

Intellectual function (IQ) was assessed using the Wechsler Abbreviated Scale of Intelligence- Second edition (WASI-II). Two subtests (vocabulary and matrix reasoning) of the WASI-II were administered to derive an estimate of IQ (Wechsler, 2011).

4.3.2.2. Experience sampling of mind wandering

Experience sampling of MW was carried out eight times daily, across five consecutive days. We used an iOS app called MoodMapper, designed for the investigation of emotional dysregulation and MW by co-authors CR and PA. MoodMapper was uploaded onto Apple iPods with all other functions disabled. Signals for the onset of each monitoring period were provided by Vibralite 12 wristwatches that were synchronised with the iPods, giving silent vibration signals eight times a day, at the onset of each rating period. Participants were instructed to complete each rating based on the time-period just before the signal. Following the protocol of Skirrow et al. (2014), signals occurred following a pseudorandomised schedule, with a minimum inter-rating interval of 65 minutes and a maximum interval of 135 minutes (around 10 hours of data collection each day). Participants started the ESM phase the day after their research appointment. Start and end times were the same each day.

Several steps were implemented to promote compliance and were incorporated into the testing protocol, including telephone calls to prompt participants when they were required to start monitoring, a follow-up call during the monitoring week, providing a 'mood monitoring hotline' telephone number and e-mail address, and an instruction leaflet.

ESM ratings focused on three parameters of daily subjective MW experience: (1) intensity of MW, (2) instability of MW over time, and (3) content of MW (something pleasant/unpleasant). The use of ratings eight times per day over five days enabled an evaluation of the dynamic process of MW, capturing changes in MW over time. MoodMapper employed a total of seven MW questions (see Table 4.1 for details): five items that used a continuous visual analogue scale with ratings ranging from 0 (not at all) to 100 (extremely) and two categorical items.

Table 4.1 Description of MW items in the MoodMapper

Items	Description	Scoring
Item1	How much is your mind on what you are doing or elsewhere NOW?	0……...100
Item2	Were you thinking about many different things at once NOW?	0……...100
Item3	How often do new thoughts keep popping into your head NOW?	0……...100
Item4	How hard is it to stick your thoughts to one thing at a time?	0……...100
Item5	My mind just goes-I cannot switch it off	0……...100
Item6	What are you thinking about NOW?	a. What I am doing b. Daydreaming about something else c. My mind drifted off and I can't remember
Item7	Are you thinking about something other than what you are doing NOW?	a. No b. Yes, daydreaming about something pleasant c. Yes, daydreaming about something unpleasant d. Yes, daydreaming about something neutral e. Yes, daydreaming but can't remember

4.3.2.3 Pre-processing of ESM data

Data inspection was completed before analyses to check for distributions, outliers and implausible data. All reports not completed within 16 minutes after the vibration signal were excluded from analyses. Compliance rates for each participant were

obtained by identifying the proportion of monitoring instances (maximum 40: eight ratings per day, over five days) completed within the 16-minute window. In line with previous studies (Simons et al., 2009; Skirrow et al., 2014), participants with an overall compliance rate less than 40% were excluded from the analyses (n=7).

To obtain a measure of MW variability, we calculated squared successive differences (SSD), a well-established procedure in experience sampling studies (Ebner-Priemer et al., 2007), for each of the continuous MW items. SSD was calculated by taking the squared value of the difference between successive responses: $SSD=(t_i-t_{i-1})^2$. The SSD emphasizes larger changes (Trull et al., 2008) and incorporates aspects of amplitude (the degree of change), frequency (the rate of change) and temporal dependency (the sequence in which reports are made), and is robust to systematic time trends in time series data (Jahng, Wood, & Trull, 2008). Further details on the pre-processing of ESM data are provided in section 2.6.2 in chapter 2.

4.3.3 Statistical analyses

Analyses were carried out in SAS University edition- virtualbox and SPSS 24. The significance level α was set at 0.05 (two-tailed). In our multilevel models, adjustments per item for multiple testing contrast tests were made by applying Bonferroni and Bonferroni-Holm corrections. However, no adjustment was reported for multiple measures of MW as these were highly correlated (see section B in supplementary 4). Mean ratings were computed for questionnaire based self-report measures and compared between groups. For simple group comparisons, normality of data was assessed graphically by examining histograms and QQ plots, and with the Shapiro-Wilk statistic. Parametric and non-parametric tests were used, as appropriate.

For analysis of the ESM data, multilevel models were used to take into account correlated observations nested within individuals, and perform well with missing data (Jahng et al., 2008). Instead of the conventional predefined diagnostic group comparisons, we used two new binary categorical grouping variables indicating the presence or absence of ADHD and BPD diagnoses separately for each individual.

We used these new variables as predictors in the analyses of a 2x2-model with two main effects of ADHD and BPD and the interaction ADHD*BPD (assuming non-

additivity of the ADHD and BPD effects). We then investigated differences across diagnoses by contrasts according to the a priori hypotheses expressed above: (1) intensity of MW using raw data, and (2) instability of MW ratings using SSDs. Normally distributed data were analysed with a linear mixed model with a random intercept (SAS procedure MIXED). SSDs follow a χ^2 distribution, which is a special case of the gamma distribution and were analysed with a series of generalised multilevel models with gamma distributions and log links (SAS procedure GLIMMIX). Categorical data exploring frequency of MW occurrence, MW awareness and content of MW were analysed using multilevel logistic regression models with a binary distribution in the SAS procedure GLIMMIX.

As MW has been previously associated with mood disorders, such as depression, anxiety (Christoff et al., 2016; Hoffmann et al., 2016; Xu et al., 2017), and unhappiness (Killingsworth & Gilbert, 2010), and given the significant co-occurrence of comorbid depression and anxiety in both ADHD and BPD populations (Cumyn, French, & Hechtman, 2009; Zanarini et al., 1998), we explored potential confounding effects of depressive and anxious symptomatology on MW; where significant bivariate associations were detected, models were adjusted accordingly.

4.3.4 Ethical standards

All participants gave full informed consent. The National Research Ethics Service Committee London – London Bridge, granted research ethics approval for this study (reference: 15/LO/1280).

4.4 Results

4.4.1 Sample characteristics and compliance

The sample consisted of 98 participants: 28 participants with ADHD (M_{age}=38.2, SD=11.7), 19 with BPD (M_{age}=35.4, SD=11.4), 22 with comorbid ADHD/BPD (M_{age}=33.8, SD=13.8), and 29 controls (M_{age}=27.1, SD=5.2). There was a statistically significant group differences on age, $X^2(3) = 14.18$, p=.003 and IQ, F (3,93) = 4.6. p=.005 (ADHD: M=106.5, SD=14.2; BPD: M=97, SD=13.8; ADHD/BPD: M=97.7, SD=12.4; controls: M=107.2, SD=9.2). Both age and IQ

were initially controlled for in subsequent analyses but did not have a significant effect in the models. Therefore, we reported the models by excluding these covariates. The groups did not show a difference in the compliance rate of ESM ratings: percentage of valid completion of ESM ratings ($X^2(3) = .12$, $p = .989$) with a mean of 74.8% and SD of 14.9 across the whole sample.

4.4.2 Mind Excessively Wandering Scale

The non-parametric Kruskal-Wallis test showed a significant effect of group on the MEWS, $X^2(3) = 58.06$, $p < .001$. Bonferroni adjusted post-hoc tests revealed that controls (mean rank= 16.2) reported significantly less MW, $p < .001$, than ADHD (mean rank=66.7), BPD (mean rank=56.4) and comorbid ADHD/BPD (mean rank=65.4). However, there were no significant differences between clinical groups ($p = 1$). When adjusting for BSI scores of anxiety and depression, differences only between ADHD and comorbid ADHD/BPD remained non-significant ($p = .558$).

4.4.3 Group differences on ESM ratings

4.4.3.1 Intensity

For the continuous measures of MW, multilevel models revealed significant interaction effect of ADHD*BPD ($p < .01$) for all five items with significantly elevated intensity of MW in all clinical diagnoses compared to controls, when no adjustments were made for covariates (see model 1, Table 4.2). When adjustments were made for BSI anxiety and depression scores, models also revealed significant interaction effect of ADHD*BPD ($p < .01$) for all five items but there only remained significant differences between controls and ADHD for all the items except item-5 (see model 2, Table 4.2) (see section C in supplementary 4 for results of the interactions per item).

Table 4.2 Differences between diagnostic groups and control group on MW intensity as estimated by multilevel modelling

Intensity	Model parameters for group	No diagnosis vs ADHD diagnosis		No diagnosis vs BPD diagnosis		No diagnosis vs comorbid ADHD/BPD diagnosis	
		Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Item1	Estimate	-22.93	-18.5	-20.14	-12.23	-21.75	-11.43
	S.E	4.16	4.53	4.64	6.13	4.44	6.67
	p value	**<.001**	**<.001**	**<.001**	.242	**<.001**	.357
Item2	Estimate	-27.88	-19.86	-19.77	-5.81	-25.04	-6.74
	S.E	4.46	4.52	4.97	6.03	4.76	6.52
	p value	**<.001**	**<.001**	**<.001**	.908	**<.001**	.908
Item3	Estimate	-30.57	-22.11	-22.2	-5.63	-25.62	-4.52
	S.E	4.59	4.72	5.11	6.22	4.89	6.68
	p value	**<.001**	**<.001**	**<.001**	1	**<.001**	1
Item4	Estimate	-35.79	-28.01	-27.9	-13.42	-32.13	-13.46
	S.E	4.37	4.4	4.88	5.86	4.67	6.32
	p value	**<.001**	**<.001**	**<.001**	.071	**<.001**	.071
Item5	Estimate	-38.46	-31.24	-30.94	-17.99	-36.93	-20.09
	S.E	5.13	5.2	5.72	6.76	5.47	7.2
	p value	**<.001**	**<.001**	**<.001**	**.035**	**<.001**	**.030**

Model 1: Multilevel models unadjusted
Model 2: Multilevel models adjusted for BSI anxiety and depression scores

Multilevel models revealed no significant differences between clinical diagnoses on intensity of MW, when no adjustments were made for covariates (see model 1, Table 4.3). When adjustments were made for the BSI anxiety and depression scores, where only anxiety had a significant main effect in the model, significant differences between ADHD and BPD, plus ADHD and comorbid ADHD/BPD diagnosis were revealed on items 3 and 4, as well as between ADHD and BPD on item 2, whereby the ADHD group had heightened reports of MW intensity compared to BPD and comorbid ADHD/BPD (see model 2, Table 4.3). There were no significant differences between BPD and comorbid ADHD/BPD diagnoses, even after adjusting for anxiety and depression (see section D in supplementary 4 for estimated means).

Table 4.3 Between-diagnoses differences on MW intensity as estimated by multilevel modelling

Intensity	Model parameters for group	ADHD diagnosis vs BPD diagnosis		ADHD diagnosis vs comorbid ADHD/BPD diagnosis		BPD diagnosis vs comorbid ADHD/BPD diagnosis	
		Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Item1	Estimate	2.79	6.28	1.19	7.08	-1.6	0.8
	S.E	4.67	5.27	4.48	5.51	4.92	4.94
	p value	1	.606	1	.606	1	.872
Item2	Estimate	8.11	14.06	2.84	13.12	-5.27	-0.93
	S.E	5.01	5.24	4.8	5.45	5.28	4.95
	p value	.326	**.043**	.641	.070	.641	.908
Item3	Estimate	8.37	16.48	4.95	17.59	-3.42	1.11
	S.E	5.15	5.46	4.93	5.64	5.42	5.2
	p value	.322	**.013**	.636	**.011**	.636	1
Item4	Estimate	7.89	15.17	3.66	14.55	-4.23	-0.1
	S.E	4.91	4.79	4.7	5.29	5.17	4.82
	p value	.334	**.026**	.831	**.028**	.831	.994
Item5	Estimate	7.52	13.25	1.53	11.15	-5.99	-2.1
	S.E	5.76	6.03	5.52	6.16	6.07	5.79
	p value	.585	.090	.782	.146	.652	.717

Model 1: Multilevel models unadjusted
Model 2: Multilevel models adjusted for BSI anxiety and depression scores

4.4.3.2 Instability

Multilevel models revealed a significant interaction effect of ADHD*BPD ($p \leq .01$) only for item-5 with ($F(1, 92.82) = 4.96$, $p = .028$) and without ($F(1, 91.58) = 4.87$, $p = .030$) adjustment for anxiety and depression. Contrast tests showed there were no significant differences between clinical diagnoses and controls on items 1, 2, 3, and 4 (see Table 4.4). Controls reported significantly less instability of MW rated on item-5 compared to all clinical diagnoses ($p < .05$). Despite item-5 being highly correlated with all other ESM items (see section B of supplementary 4 for inter-item correlations), the significant difference could still reflect a type II error. There were no between-diagnoses differences found on all items (see section E of supplementary 4) for instability of MW. All groups showed similar levels of instability. Anxiety and depression had no effect in the instability models and the adjusted results are therefore not presented here.

Table 4.4 Differences between diagnostic groups and control group on MW instability as estimated by multilevel modelling

Instability	Model parameters for group	No diagnosis vs ADHD diagnosis	No diagnosis vs BPD diagnosis	No diagnosis vs comorbid ADHD/BPD diagnosis
Item1	Estimate	-0.53	-0.37	-0.46
	S.E	0.26	0.29	0.28
	p value	.298	.871	.522
Item2	Estimate	-0.62	-0.52	-0.52
	S.E	0.28	0.32	0.3
	p value	.190	.454	.454
Item3	Estimate	-0.65	-0.47	-0.66
	S.E	0.26	0.29	0.28
	p value	.086	.440	.095
Item4	Estimate	-0.61	-0.62	-0.52
	S.E	0.27	0.3	0.29
	p value	.153	.202	.290
Item5	Estimate	-1.13	-1.19	-1.19
	S.E	.33	.37	.35
	p value	**.005**	**.006**	**.005**

4.4.3.3 Frequency of occurrence, awareness and content of MW

For the categorical measure of the frequency of MW occurrence (see item 6 in Table 4.1), multilevel logistic regression models revealed a significant interaction effect of ADHD*BPD (F (1, 80.66)= 6.49, p=.013) with all clinical diagnoses reporting greater frequency of MW compared to controls (p<.001), with an OR[2] of 3.9 (CI:1.7-9.3) for BPD diagnosis versus control, 3.9 (CI:1.8- 8.3) for ADHD diagnosis versus control and 5.2 (CI:2.3- 11.6) for comorbid ADHD/BPD diagnosis versus control. However, when the models were adjusted for anxiety and depression, despite the significant interaction effect of ADHD*BPD (F (1, 79.73)= 5.08, p=.027), significant differences between controls and BPD diagnosis (p=.142) as well as controls and comorbid ADHD/BPD diagnosis dissipated (p=.142), and only the ADHD diagnosis still reported more frequent MW compared to controls (p=.005), with an OR of 2.9 (CI:1.2- 6.7). However, there were no differences in the frequency of MW occurrence among clinical diagnoses, even after controlling for the covariates (p=1).

When participants reported that their minds were wandering, we investigated the extent to which they were aware of this phenomenon (see item 6 in Table 4.1). There

[2] OR: Odds ratio

was no significant interaction effect of ADHD*BPD with (p=.387) and without (p=.466) adjusting for anxiety and depression on awareness of MW. Contrast tests showed that there were significantly elevated rates of MW without awareness only in the comorbid ADHD/BPD diagnosis compared to controls with (p=.009; OR=.1; CI: .01-.7) and without (p=.002; OR=.2; CI: .01-.7) controlling for anxious and depressive symptomatology. However, there were no differences in MW awareness among clinical diagnoses, even after controlling for the covariates (p>.05).

Regarding the content of MW (see item 7 in Table 4.1), our models revealed non-significant interaction effects of ADHD*BPD with (p=.760) and without (p=.497) adjusting for anxiety and depression. Contrast tests revealed significantly elevated rates of MW about 'something unpleasant' in the BPD (p=.017; OR=.3; CI: .1-.9) and comorbid ADHD/BPD (p=.017; OR=.3; CI: .1-.9) diagnosis compared to controls, whereas no differences were seen between ADHD and controls (p=.806). When the multilevel logistic models were adjusted for anxiety and depression, these differences between controls and BPD diagnosis (p=1), as well as controls and comorbid ADHD/BPD diagnosis (p=1) disappeared. However, no differences were found in the proportion of MW about "something unpleasant" between clinical diagnoses (p>.05), even after accounting for anxiety and depression (p=1).

4.5 Discussion

The main aim of this study was to investigate similarities and differences in measures of MW in ADHD, BPD, comorbid ADHD/BPD and controls. We first used a rating scale measure of excessive MW developed by our group and shown to be sensitive to the ADHD diagnosis. We then applied a more objective method, ESM, to investigate different aspects of MW in daily life: examining heightened frequency, intensity and instability of MW. We further investigated the proportion of MW with and without awareness (meta-awareness), and the proportion of negative thought content during periods of MW with awareness.

Overall, we found heightened levels of MW in all the clinical diagnoses compared to controls using both the MEWS scale of excessive spontaneous MW, and ESM measures of MW intensity. However, when controlling for anxiety and depression

symptoms, the differences between controls and BPD diagnosis, as well as between controls and comorbid ADHD/BPD diagnosis dissipated, with only ADHD diagnosis showing significantly elevated MW intensity compared to controls.

Consistent with these effects, we found no differences in MW intensity between the clinical diagnoses. However, after controlling for anxiety and depression symptoms, ADHD diagnosis showed significantly elevated intensity of MW compared to BPD and comorbid ADHD/BPD on most items, while there were no differences between BPD and comorbid ADHD/BPD diagnoses.

The results from the categorical variable exploring frequency of MW occurrence supported these findings. While all three clinical diagnoses reported more frequent MW than controls, the significance only persisted between controls and the ADHD diagnosis, but not BPD nor comorbid ADHD/BPD, when symptoms of depression and anxiety were controlled for.

The absence of MW instability differences amongst clinical cases as well as cases versus controls suggests that MW reflects a stable phenomenon over time, irrespective of the presence or absence of a clinical diagnosis. While this might be explained by a relatively low sampling frequency in this study, these findings suggest that mean differences in the frequency and intensity of MW, rather than instability, characterise pathological forms of MW.

With regard to ADHD, these findings suggest that MW (independent of anxiety and depression) is a core characteristic of the disorder, supporting the view that MW reflects a core process in ADHD (Bozhilova et al., 2018). This is in line with previous findings of elevated MW in ADHD compared to controls (Mowlem et al., 2016). Following the findings from Van den Driessche et al. (2017) we also hypothesised that during periods of MW, there would be a greater proportion of MW without awareness associated with the ADHD diagnosis. However, we only found that the comorbid ADHD/BPD diagnosis was associated with a greater proportion of MW without awareness compared to controls, potentially reflecting greater severity of MW in the comorbid ADHD/BPD diagnosis. This may arise since MW without awareness is thought to reflect a more severe form of MW, with greater disruption of the neural regulation processes involved (Bozhilova et al., 2018).

Finally, the data supported the hypothesis that in ADHD the content of MW would reflect the same proportion of pleasant to unpleasant thoughts as that seen in controls. This is in line with the clinical observation that while the form of thought (i.e. excessive MW) may differ in ADHD, content of thought is comparable to that seen in most other people who do not have a mental illness (Asherson, 2005).

The finding of similar levels of MW in BPD to that seen in ADHD was unexpected, raising the possibility that excessive MW leading to inattentiveness may be a greater problem in the daily lives of people with BPD than generally recognised. However, in BPD the association with MW was driven by anxious and depressive symptoms, suggesting that excessive MW may be secondary to co-occurring anxiety and depressive symptoms. This was further supported by the finding that without adjusting for anxiety and depression scores, MW about something unpleasant was higher in BPD and comorbid ADHD/BDP compared to controls, whereas no differences appeared between ADHD and controls. However, when controlling for anxiety and depression symptoms the differences between BPD and comorbid ADHD/BPD and controls dissipated. This suggests that MW about something unpleasant may reflect anxious thoughts or depressive ruminations in BPD, but not in ADHD. However, the lack of significance in the content of MW between the clinical diagnoses reduces confidence in this conclusion, which requires further investigation.

Our finding of excessive MW in BPD differed from a previous report which found no increase in the frequency of MW in BPD during a choice reaction time task (Kanske et al., 2016). This might be explained by using ESM in daily life rather than during a laboratory computer task or could be related to greater levels of anxiety and depression in our sample.

Overall our results show that although excessive MW is common in both ADHD and BPD, the source of MW may differ. For example, being related to different triggers and internal or external mechanisms. A recent review hypothesises that in ADHD, excessive spontaneous MW may reflect a core problem related to a failure of the default mode network (DMN) deactivation during task conditions, reflecting dysfunctional interactions between DMN and salience and cortical control networks

(Bozhilova et al., 2018). Such heightened DMN activity may lead to periods of spontaneous MW that interfere with attention to external task, underlying the symptoms and impairments of ADHD.

In contrast, social threat hypersensitivity is a core characteristic of BPD patients, who show heightened attention to perceived threat (Bertsch et al., 2013). Therefore, we can speculate that the combination of a higher tendency to overestimate social threat from ambiguous cues, together with difficulties in relational functioning (Kaiser, Jacob, Domes, & Arntz, 2017), increases feelings of resentment and anxiety leading to alternative forms of MW such as anxious worrying and depressive ruminations. This is consistent with higher levels of negative thoughts during periods of MW in BPD seen in this study, and the high levels of anxiety and depressive symptoms seen in people with BPD (Stepp, Scott, Jones, Whalen, & Hipwell, 2016).

Although we have drawn attention to differences in the characteristics of MW in ADHD and BPD, the overall conclusion is that excessive MW is seen equally in both disorders. This is not entirely surprising since there are brain structural and functional commonalities between ADHD and BPD in the salience and executive control networks (Xenaki & Pehlivanidis, 2015) and previous studies report similar types of altered functioning of the DMN both in ADHD (Fassbender et al., 2009; Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2015) and BPD (Wolf et al., 2011; Yang, Hu, Zeng, Tan, & Cheng, 2016). This may explain excessive MW in both disorders since the degree of DMN deactivation has been proportionately linked to the frequency of self-generated task-unrelated thoughts (Christoff et al., 2016; Kucyi, Esterman, Riley, & Valera, 2016; Smallwood, Brown, Baird, & Schooler, 2012).

The relationship between increased spontaneous MW and ADHD symptomatology is now well established in the literature (Franklin et al., 2014; Mowlem et al., 2016; Seli et al., 2015). Regarding BPD, in addition to the potential functional alterations of DMN connectivity during resting state similar to ADHD (Wolf et al., 2011; Yang et al., 2016), previous research shows that individuals with BPD often cope with their intense negative emotions by suppressing them (Scheibner et al., 2016). Cognitive suppression of intrusive and unwanted thoughts or images that usually involve a high

emotional burden (Wegner & Zanakos, 1994), paradoxically, would often result in greater access to such thoughts (Wegner & Erber, 1992). In addition the tendency to suppress these thoughts has been associated with increased sympathetic activation, increased anxiety and depression, and an increased risk of emotional disturbance (Wenzlaff & Wegner, 2000). Consequently, it seems plausible to assume that this same phenomenon is partially contributing to MW in BPD.

This study was the first to compare ADHD and BPD for measures of MW. Although we used multiple measures of MW and included carefully selected and diagnosed clinical groups, there are several limitations to consider. First, the sample was comprised of females only. This has the advantage that we did not have to account for potential sex differences in our analyses, but also means that the findings cannot be generalised to males. Considering excessive spontaneous MW as a core characteristic of ADHD, we should not ignore the possibility that a different pattern of MW may be found for females and males. In BPD, women have been reported to ruminate more than men (Johnson & Whisman, 2013). Further studies are required to confirm these findings in males.

Depression and anxiety were measured by the BSI, a self-report scale, which has varied evaluations about its validity. Previous confirmatory factor analyses have shown high intercorrelations among the BSI subscales, suggesting that the BSI could be a better general indicator of psychopathology rather than a screening tool for each of the subscales separately (Boulet & Boss, 1991; Wang et al., 2010). We should therefore consider this limitation before drawing strong conclusions about the relationship of MW and anxiety and depression in BPD.

Despite having an acceptable compliance rate for the ESM ratings, further studies exploring the specificity of MW in ADHD and BPD using an experience sampling approach could benefit from larger sample sizes.

Regardless of these limitations, our findings suggest that excessive spontaneous MW is a transdiagnostic process present in both ADHD and BPD. Yet, different processes may drive the underlying mechanisms of this subjective experience. Research on the specific cognitive and neurobiological mechanisms associated with MW should be investigated both in ADHD and BPD, to explain the underlying

causes of the clinical overlap between ADHD and BPD. The strong association of anxiety and depression with MW in BPD only should be further explored in the context *of* delineating different aetiological subtypes of MW. An analogy is fever, which like MW is a symptom seen across conditions but reflecting different underlying specific causes. This analogy could be further extended to treatment of *MW and* related impairments. It has been suggested that treatment of ADHD with methylphenidate might be mediated by reductions in MW (Mowlem et al., 2016). Moreover, it is assumed that methylphenidate improves focus and enhances executive resources, as well as enhances task-related DMN deactivation (Van den Driessche et al., 2017), which in turn could reduce MW. Whether methylphenidate would reduce excessive MW in other conditions such as BPD is however entirely unknown, requiring further studies. Thus, further critical work is required to disentangle the relationship between ADHD and BPD, leading to more accurate diagnoses and, targeting of treatments.

Chapter 5: A comparative investigation of emotional dysregulation in ADHD and borderline personality disorder using an experience sampling approach

5.1 Abstract

Emotional dysregulation is a core diagnostic symptom in borderline personality disorder (BPD) and has been described as frequently co-occurring with attention-deficit/hyperactivity disorder (ADHD). The current study attempted to qualitatively distinguish ADHD and BPD on the dynamic construct of emotional changes by using ambulatory monitoring of negative and positive emotions (sad, irritable, angry, happy and excited) and retrospective measures in adult females with ADHD, BPD, comorbid ADHD/BPD and healthy controls.

Individuals with ADHD and BPD reported some differences in the intensity and instability of negative emotions, which were fully accounted for by symptoms of depression and anxiety. Neither the increased intensity nor instability in emotions in the clinical diagnoses could be fully accounted for by increased frequency and impact of bad events, reflecting both a reactive and an endogenously driven component of emotional dysregulation in both ADHD and BPD. In line with previous studies using ambulatory assessments in psychiatric populations, small to moderate correlations were found between indices of emotional dysregulation from ambulatory assessment and those from retrospective measures. Findings suggest that ambulatory monitoring can provide conclusions, which are not equivalent but complementary to rating scale measures.

This study supports the notion that emotional dysregulation is a transdiagnostic clinical symptom present in both ADHD and BPD and could not be used to distinguish between the disorders.

5.2 Introduction

The differential diagnosis of attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) is important for the accurate treatment and management of both conditions. Yet, overlapping symptoms, notably symptoms of emotional dysregulation, can make differentiation of the conditions challenging. According to the DSM-5, emotional dysregulation reflects a core symptom domain in the diagnostic classification of BPD, whereas in ADHD it is recognised as an

associated feature supporting the diagnosis (American Psychiatric Association, 2013).

Emotional dysregulation is a dimensional construct (Shaw, Stringaris, Nigg, & Leibenluft, 2014) and is characterised by problems with temper control (feelings of irritability and frequent outburst of short duration), emotional over-reactivity (diminished ability to handle typical life stresses, resulting in frequent feelings of being hassled and overwhelmed), and mood lability (short and unpredictable shifts from normal mood to depression or mild excitement) (Reimherr et al., 2005).

Emerging evidence shows that emotional dysregulation is present in 72–90% of adults with ADHD, and independently of core symptoms of ADHD predicts impairments in social, educational and occupational domains (Asherson, 2005; Skirrow et al., 2014), and responds to treatment within the same time-frame as core ADHD symptoms in adults (Rosler et al., 2010). In contrast, emotional dysregulation is one of the core symptom domains of individuals with BPD, who nearly always suffer from severe persistent affective instability, inner tension and difficulty controlling emotions such as anger (American Psychiatric Association, 2013).

Phenomenologically, emotional dysregulation is a complex construct, with shared characteristics in both ADHD and BPD, particularly pertaining to feelings of heightened and unstable reactivity of mood, and difficulty controlling anger (criterion six and eight for BPD diagnosis respectively) (Moukhtarian, Mintah, Moran, & Asherson, 2018). It remains unclear whether the type of emotional dysregulation seen in ADHD is qualitatively similar or different from that seen in BPD (Moukhtarian et al., 2018).

One way to investigate this dynamic and time-dependent process over time (Carpenter & Trull, 2013) is by ambulatory assessments, a gold standard method that assesses this longitudinal within-individual changing (i.e. direct measure of instability) phenomenon (Ebner-Priemer & Sawitzki, 2007; Solhan, Trull, Jahng, & Wood, 2009). Ambulatory assessments are repeated assessments over time that include a range of methods to study individuals' affective states, behaviours or physiological processes in their natural environment (Santangelo, Bohus, & Ebner-

Priemer, 2012; Trull & Ebner-Priemer, 2014). Ambulatory assessment, diary methods, ecological momentary assessment or experience sampling method (ESM) are different terms often used interchangeably in the literature (Trull & Ebner-Priemer, 2014). They all encompass methods that can provide multiple assessments of mood per day over several days measuring change of affect from one moment to the next, yielding to intensive longitudinal data (Carpenter & Trull, 2013). In this study, the method will be referred to as ESM.

By providing real-time assessments, ESM minimises retrospective and heuristic biases (Ebner-Priemer et al., 2006; Santangelo et al., 2012). In fact, it is suggested that the recollection of emotional situations are heavily influenced by the most intense point of the event and the end-point state, known as the 'peak-end' rule (Santangelo et al., 2012). In disorders like BPD, where a symptom is defined by rapid swings in mood, once-a-day diary entries or even retrospective questionnaire entries don't take into account the timely nature of the data nor the affective changes within the day (Santangelo et al., 2012). In addition, ESM assessments take place in people's natural environments where assessments are more ecologically valid and therefore generalisable to real life, as opposed to questionnaire data collected in artificial laboratory or clinical settings (Carpenter & Trull, 2013; Santangelo et al., 2012). Finally, data based on clinical interviews are often dependent on the skills of the interviewers or raters; another bias issue not seen in ESM studies (Trull & Ebner-Priemer, 2014).

Ambulatory assessments have been used to measure unstable emotions and a variety of clinical conditions and symptoms in different psychiatric illnesses, including negative affect in depressive disorders (Chepenik et al., 2006), depressive symptoms in bipolar disorder (Bauer et al., 2007), affective instability in bulimia nervosa and post-traumatic stress disorder (Santangelo et al., 2014), affective intensity and instability in ADHD (Skirrow et al., 2014) and distress in BPD (Ebner-Priemer, Kuo, et al., 2007) among others.

To date, only one ESM study has investigated the dynamics of emotional dysregulation in adults with ADHD (Skirrow et al., 2014). Compared to controls (n= 47), patients with ADHD (n= 41) showed significantly increased instability of

irritable, *frustrated* and *angry* and increased intensity of *irritable* and *frustrated*. They also showed greater reactivity of negative emotions, such as anger, to 'bad' life events. In addition, compared to controls, patients with ADHD showed no differences in the intensity and instability of positive emotions (happy, excited). This study included only males and specifically excluded patients with comorbid conditions (Skirrow et al., 2014), hence attributing the heightened mood dysregulation to the presence of ADHD only.

In BPD, several ESM studies have been reported investigating emotional dysregulation. Below is a brief summary of the most recent findings.

In one study of 50 individuals with BPD and 50 psychiatrically healthy female controls, affective instability was assessed every 10-20 minutes during the waking hours of a 24-hour period (Ebner-Priemer, Kuo, et al., 2007; Ebner-Priemer et al., 2008; Ebner-Priemer et al., 2006; Ebner-Priemer, Welch, et al., 2007; Reisch, Ebner-Priemer, Tschacher, Bohus, & Linehan, 2008). The BPD group showed heightened affective instability (emotions including happy, anxious, angry, sad, disgust) characterised by rapid fluctuations from positive valence mood to negative valence mood compared to controls. BPD patients also displayed greater frequency and intensity of negative emotions compared to controls. However, no group differences were seen in the intensity of positive emotions. Moreover, when comparing retrospective questionnaire ratings to ESM ratings, results showed that the BPD group overestimated emotions with negative valence and underestimated emotions with positive valence when using rating scales data, contrary to the control group who did the opposite.

In another all-female study comparing 76 outpatients with BPD and 50 controls with a depressive disorder, affective states were recorded using ESM six times a day over a 28-day period (Jahng et al., 2011; Jahng, Wood, & Trull, 2008; Solhan et al., 2009; Trull et al., 2008). Overall, results indicated greater instability over time for fear, hostility and sadness in the BPD group only. Results also showed an increased long-term (between-day) and short-term (within-day) instability of negative affect in BPD compared to patients with a depressive disorder.

In a female-only study using a paper-and-pencil diaries and an event-contingent sampling strategy over a 20-day period, authors reported heightened instability in pleasant affect (happy, pleased, fun, joyful) for patients with BPD (n=38) compared to healthy controls (n=44), but interestingly no group differences in the instability of negative affect (anxious, frustrated, angry, unhappy, sad) (Russell, Moskowitz, Zuroff, Sookman, & Paris, 2007; Sadikaj, Russell, Moskowitz, & Paris, 2010).

Finally, in a more recent study, Santangelo et al. (2014) investigated the specificity of affective instability in BPD (n=43), compared to posttraumatic stress disorder (PTSD) (n=28), bulimia nervosa (n=20), and healthy controls (n=28), approximately every 15 minutes for 24-hours. Findings showed that affective instability was equally heightened in all patient groups (Santangelo et al., 2014). Contrary to Santangelo et al., Scheiderer et al. (2016) employed ESM six times a day over a 28-day period and found significant differences in the instability of negative affect across the BPD with and without PTSD (n=78), and psychiatric comparison groups of major depressive disorder (n=50).

To date, the empirical findings from the above-mentioned ESM studies show some inconsistencies because of various methodological and statistical differences. However, overall, they point to heightened instability of negative emotion reported by both retrospective scales and ESM methods for both BPD and ADHD. Although a strong relationship between ADHD and BPD pertaining to overlapping symptoms of emotional dysregulation has been established using retrospective measures (Bernardi et al., 2012; Cumyn, French, & Hechtman, 2009; Ferrer et al., 2010; Jacob et al., 2007; Philipsen et al., 2008; Speranza et al., 2011), no direct comparison has assessed the overlapping dynamic construct of emotional dysregulation using ESM in naturalistic settings.

The present study investigated the dynamics of positive and negative emotions, and the occurrence and impact on mood of bad social and functional events (described in section 5.3.2.2), captured by ESM eight times a day, over five days in adult females with ADHD, BPD, comorbid ADHD/BPD, and psychiatrically healthy controls. By taking an exploratory approach, I investigated whether there were any differences in the intensity and instability of positive and negative emotions in ADHD and BPD, first using retrospective questionnaire-based data, and secondly

using ESM measures of mood in everyday life. I also hypothesised that reactivity of negative mood will predominantly be influenced by bad social events (i.e. involving other people or events in social situations) in BPD, whereas in ADHD, negative mood will be impacted more frequently by bad functional events (i.e. in relation to practical and everyday life tasks). Finally, to examine the strength of association between ambulatory assessments of emotions with more conventional retrospective self-report measures of emotional dysregulation, I cross-validated the two measures to establish whether the scales reflect the same construct as the ESM data.

5.3 Methods

5.3.1 Sample

98 female participants aged of 18-65 years (M=33.4, SD=11.3) were recruited for this study. Controls, not meeting criteria for ADHD or BPD, were recruited through advertisements in King's College London, volunteer databases, and within the local community. Clinical cases were recruited from ADHD and borderline personality specialist clinics in the South and North London and Midland regions of England. Members of the clinical care teams identified potentially eligible participants and referred them to the research team. Clinician diagnoses were based on DSM criteria for ADHD and BPD (American Psychiatric Association, 2013), and validated for research by members of the research team using the Diagnostic Interview for ADHD in Adults (DIVA) (Kooij, 2013) and the Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD) (Zanarini, 2003) to maintain reliability and consistency of diagnosis across the whole sample (see section 2.3.3.1 in chapter 2 for details on clinical diagnosis). Co-morbidities were excluded using a checklist of common mental health conditions by screening clinical case records. Exclusion criteria for the clinical and control groups were: male gender; history of bipolar I and II, recurrent depressive episodes, and schizophrenia; current Axis I disorders; head injury or neurological conditions; IQ<70; and current treatment with psychoactive medication, specifically mood stabilisers and/or anti-psychotics (except concomitant medication for non-recurrent depression). Participants on stimulant medication for ADHD were asked to come off this medication for 48 hours before the baseline assessment and the following five days during experience

sampling. Due to the frequent drug and alcohol use in ADHD (Bernardi et al., 2012; Fayyad et al., 2007; Kessler et al., 2006) and BPD (Fyer, Frances, Sullivan, Hurt, & Clarkin, 1988; Zanarini, Gunderson, Frankenburg, & Chauncey, 1989) populations, I excluded individuals with addiction disorders, but not for elevated alcohol and drug use (see section 2.4.1.6 in chapter 2 for more details, and section A in supplementary 5 for sensitivity analyses).

5.3.2 Measures

5.3.2.1 Symptom measures

Emotional dysregulation was assessed using one self-rated questionnaire and one investigator-rated interview scale; the Affective Lability Scale- Short form (ALS-SF- Appendix 3) (Oliver & Simons, 2004) and the Wender-Reimherr Adult Attention Deficit Disorder Scale- Emotion dysregulation subscale (WRAADDS-EDS- Appendix 5) (Wender, 1995) respectively. Comorbid depression and anxiety were measured by the Brief Symptom Inventory (BSI) (Derogatis, 1993). All scales are described in detail in chapter 2 (section 2.4.1.1). Intellectual function (IQ) was assessed using the Wechsler Abbreviated Scale of Intelligence- Second edition (Wechsler, 2011).

5.3.2.2 Experience sampling of emotions

Experience sampling of emotions was carried out eight times daily, across five consecutive days. We used an iOS app called MoodMapper, designed for the investigation of emotional dysregulation and mind wandering in ADHD. MoodMapper was uploaded onto Apple iPods with all other functions disabled. Signals for the onset of each monitoring period were provided by 'Vibralite 12' wristwatches that were synchronised with the iPods, giving silent vibrations signals eight times a day, at the onset of each rating period. Participants were instructed to complete each rating based on the time-period just before the signal. Signals occurred following a pseudorandomised schedule, with a minimum inter-rating interval of 65 minutes and a maximum interval of 135 minutes (around 10 hours of data collection each day). The rationale for using 8 times per day assessment over five days stems for the notion that emotions are transient and short-lasting

phenomena, and affective instability usually occurs within hours and not between days. Therefore, intervals that are too long might fail to detect natural changes, exclude important events, and even contribute to biased recollection. On the other hand, very short intervals could increase the burden placed on participants. There is in fact no general convention for time-based designs established to date (Ebner-Priemer & Sawitzki, 2007). Therefore, a similar protocol to that successfully implemented by Skirrow et al. (2014) in their study of adult men with ADHD and controls was followed. Participants started the ESM phase the day after their research appointment. Start and end times were the same each day. Several steps were implemented to promote compliance and were incorporated into the testing protocol, including telephone calls to prompt participants when they were required to start monitoring, a follow-up call during the monitoring week, providing a 'mood monitoring hotline' telephone number and e-mail address, and an instruction leaflet.

ESM ratings of mood were based on three parameters: (1) intensity of positive and negative mood, (2) instability of positive and negative mood, and (3) impact of bad events on negative mood. Items included emotions frequently associated with ADHD and BPD in the literature. MoodMapper employed a total of eight questions (see Table 5.1 for details): Six items used a continuous visual analogue scale with ratings ranging from 0 (not at all) to 100 (extremely), and two were categorical items.

Table 5.1 Moodmapper mood items with descriptions

Items	Description	Scoring
Item1- Happy	How **happy** do you feel now?	0……...100
Item2- Excited	How **excited** do you feel now?	0……...100
Item3- Sad	How **sad** do you feel now?	0……...100
Item4- Irritable	How **irritable** do you feel now?	0……...100
Item5- Angry	How **angry** do you feel now?	0……...100
Item6	Did any bad thing happen to you in the past hour?	1. No 2. Argument 3. Lost something 4. Late/missed something I wanted 5. Told off 6. Punished 7. Hurt/accident/pain 8. Annoyed by someone 9. Bullied 10. Failed something 11. Need to do something I dislike 12. Other
Item7	Did any good thing happen to you in the past hour?	1. No 2. Doing something well 3. Compliments 4. Rewarded 5. Being in good company 6. Doing something I like 7. Other

5.3.2.3 Pre-processing of ESM data

Data inspection was completed before analyses to check for distributions, outliers and implausible data. Allowing a choice in the self-selection of monitoring instances runs the risk of introducing each participant's bias in selecting some instances and overlooking others (Bolger, Davis, & Rafaeli, 2003). Therefore, to reduce this bias, all reports not completed within 16 minutes after the vibration signal were excluded from analyses (Skirrow et al., 2014; Solhan et al., 2009). Compliance rates for each participant were then obtained by identifying the proportion of monitoring instances (maximum 40: eight ratings per day, over five days) completed within the 16-minute window. In line with previous studies (Simons et al., 2009; Skirrow et al., 2014), participants with an overall compliance rate less than 40% were excluded from the analyses (n=7).

To obtain a measure of emotional *i*nstability, squared successive difference (SSD) for each item was calculated by taking the squared value of the difference between successive responses: SSD= $(t_i-t_{i-1})^2$. SSD emphasizes larger changes (Trull et al., 2008) and incorporates aspects of amplitude (the degree of change), frequency (the

rate of change) and temporal dependency (the sequence in which reports are made), and is robust to systematic time trends in time series data (Jahng et al., 2008). Mean SSD (MSSD) was calculated by averaging SSDs within each day and then averaging across days (Solhan et al., 2009).

Finally, multiple choice answers for the bad events question (see item 6 in Table 5.1) were grouped into two categories; (1) *bad social*: argument, told off, punished, annoyed by someone, bullied, which were events involving other people, and (2) *bad functional*: lost something, late/missed something I wanted, hurt/accident/pain, failed something, need to do something I dislike, which were events relating to everyday life situations and involving the subject only.

5.3.3 Statistical analysis

Analyses were carried out in SAS university edition- virtualbox and SPSS 24. The significance level α was held at .05 (two-tailed). In the multilevel models, adjustments per item for multiple testing contrast tests were made by applying Bonferroni and Bonferroni-Holm corrections. Adjustments across items were made for two independent sets of tests, as positive items (happy and excited), as well as negative items (sad, irritable and angry) were highly correlated, r=.80 and .70 to .80 respectively. The Bonferroni adjusted *p* for the multilevel analyses was therefore set at .025.

Mean ratings were computed for each questionnaire-based measure and compared between groups. For simple group comparisons, normality of data was assessed graphically by examining histograms and QQ plots, and with the Shapiro-Wilk statistic. Parametric and non-parametric tests were used, as appropriate.

For analysis of the ESM data, multilevel models were used to take into account correlated observations nested within individuals. These models perform well with missing data (individuals with a greater number of valid reports contribute more to the estimation of group means) (Jahng et al., 2008). Analyses investigated group differences in a 2x2-model (ADHD*BPD, assuming non-additivity of the ADHD and BPD effects), followed by contrasts according to the a priori hypotheses: (1)

intensity of emotions using raw data and (2) instability of emotions using SSDs. Normally distributed data were analysed with a linear mixed model with a random intercept (SAS procedure MIXED). SSDs follow a χ^2 distribution, which is a special case of the gamma distribution and were analysed with a series generalised multilevel models with gamma distributions and log links (SAS procedure GLIMMIX).

Additional models that specified a diagnosis-by-event interactive effects investigated whether diagnosis (ADHD and BPD) has an influence on how bad social and functional events impact negative mood.

Lastly, using Spearman's correlations a cross-validation of retrospective self-report measures of emotional dysregulation using mean scores of the ALS-SF and WRAADDS-EDS with mean instability scores (i.e. MSSD) of each ESM item was carried out.

Given the significant co-occurrence of comorbid depression and anxiety in both ADHD (Cumyn et al., 2009) and BPD (Zanarini et al., 1989) populations, potential confounding effects of depressive and anxious symptomatology on mood was explored; and where significant effects were detected, models were adjusted accordingly.

It should be noted that 31 clinical cases were on concomitant anti-depressants, which constitutes around 45% of the clinical sample. To run the main analyses without these cases, the clinical sample size would greatly decrease (ADHD= 20, BPD=4, ADHD/BPD= 14), making between group comparisons unmeaningful. Therefore, I did not run any sensitivity analyses with the exclusion of these cases.

5.3.4 Ethical standards

The National Research Ethics Service Committee London – London Bridge, granted research ethics approval for this study (reference: 15/LO/1280). All subjects participating in the study gave full informed consent.

5.4 Results

5.4.1 Participant characteristics and compliance

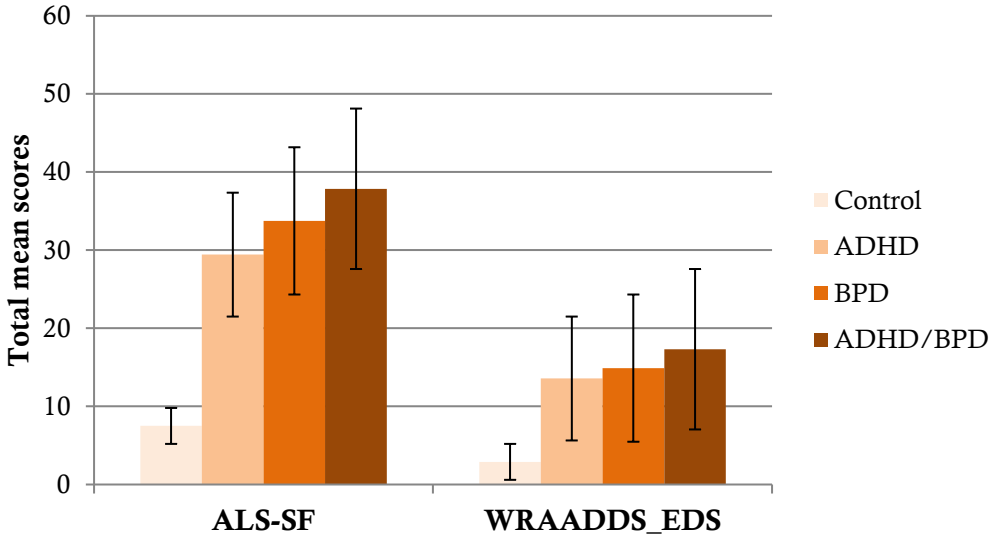
The sample consisted of 98 females between the ages of 18-65 years (M_{age}=33.42, SD=11.35), including 28 participants with ADHD, 19 with BPD, 22 with comorbid ADHD/BPD and 29 psychiatrically healthy controls. The groups significantly differed on age, $X^2(3) = 14.53$, p=.002 (ADHD: M= 38.21, SD=11.67; BPD: M= 35.45, SD=11.09; ADHD/BPD: M= 33.77, SD=13.80; controls: M= 27.14, SD=5.17), and IQ, F (3,93) = 4.6. p=.005 (ADHD: M=106.54, SD=14.19; BPD: M=97.75, SD=13.81; ADHD/BPD: M=97.71, SD=12.37; controls: M=107.21, SD=9.21). Both age and IQ were initially controlled for in subsequent analyses but did not have significant effects in the models. Therefore, I reported the models by excluding these covariates. The groups did not show a difference in the compliance rate of ESM ratings: percentage of valid completion of ESM assessments ($X^2(3)$ =.12, p=.989) with a mean of 74.8% and SD of 14.9 across the whole sample.

5.4.2 Retrospectively measured emotional dysregulation

Non-parametric Kruskal-Wallis tests revealed significant group differences in retrospective questionnaire-based emotional dysregulation ($X^2(3) = 52.22$, p< .001 for the ALS-SF, and $X^2(3) = 68.81$, p< .001 for the WRAADDS-EDS).

Post-hoc tests showed significant elevated self-ratings of emotional dysregulation in ADHD, BPD and comorbid ADHD/BPD compared to controls on both scales (p<.001). The clinical groups reported equally elevated ratings of emotional dysregulation on the ALS (p>.05). Regarding the WRAADDS-EDS, the BPD group showed similar ratings as the ADHD and comorbid ADHD/BPD groups (p> .05), but the comorbid ADHD/BPD group reported small but significantly elevated ratings compared to the ADHD group (p=.026) (see Figure 5.1).

Figure 5.1 Mean scores comparisons in retrospective emotional dysregulation scales.



Note: Error bars represent standard errors

5.4.3 Real-time emotional changes

5.4.3.1 Intensity

Multilevel models revealed a non-significant interaction effect of ADHD*BPD on all items, in unadjusted models (Model 1) and adjusted models for anxiety and depression (Model 2).

Post-hoc comparisons (see Table 5.2) revealed that the control group reported significantly higher intensity of *happy*, and significantly lower intensity of all negative emotion items (sad, irritable and angry) than the BPD and comorbid ADHD/BPD diagnoses (p<.001) (Model 1). When models were adjusted for anxiety and depression (Model 2), the significant differences between the controls and BPD as well as controls and ADHD/BPD dissipated. The control group also reported significantly elevated intensity of *excited* compared to the BPD diagnosis (p=.011) only. All comparisons were robust to Bonferroni correction (adjusted p=.025).

No differences were seen between controls and the ADHD diagnosis for the intensity of positive emotion items (happy, excited) and *angry* with and without controlling for anxiety and depression. The ADHD diagnosis compared to controls

showed heightened intensity of *sad* and *irritable* in the unadjusted models (Model 1). In the adjusted models (Model 2), significant differences only remained for *irritable* (p=.038), which was however not robust to Bonferroni correction (p=.025).

Table 5.2 Differences between diagnostic groups and control group on mood intensity as estimated by multilevel modelling

Intensity	Model parameters for group	No diagnosis vs ADHD diagnosis		No diagnosis vs BPD diagnosis		No diagnosis vs comorbid ADHD/BPD diagnosis	
		Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Happy	Estimate	4.91	-.36	20.66	5.76	19.91	2.18
	S.E	3.94	4.25	4.39	5.98	4.20	6.63
	p value	.431	1	**<.001**	1	**<.001**	1
Excited	Estimate	3.71	1.43	15.87	6.87	12.03	1.85
	S.E	4.46	5	4.97	7.05	4.76	7.81
	p value	.816	1	**.011**	1	.065	1
Sad	Estimate	-10.72	-2.01	-29.54	-4.11	-26.24	3.85
	S.E	4.64	4.56	5.17	6.43	4.95	7.13
	p value	.046	1	**<.001**	1	**<.001**	1
Irritable	Estimate	-18.52	-12.69	-27.24	-14.91	-29.93	-14.42
	S.E	4.10	4.54	4.57	6.39	4.38	7.09
	p value	**<.001**	.038	**<.001**	.110	**<.001**	.179
Angry	Estimate	-8.29	-1.89	-19.98	-5.38	-19.85	-1.78
	S.E	4.15	4.53	4.62	6.38	4.43	7.07
	p value	.097	1	**<.001**	1	**<.001**	1

Model 1: Multilevel models unadjusted
Model 2: Multilevel models adjusted for BSI anxiety and depression scores

Post-hoc comparisons (see Table 5.3) showed no group differences in the intensity of all positive and negative emotion items (happy, excited, sad, irritable, and angry) between BPD and comorbid ADHD/BPD diagnoses with and without controlling for anxiety and depression.

The ADHD diagnosis showed significantly higher intensity of *happy*, and a significantly lower intensity of *sad* and *angry* compared to the BPD and comorbid ADHD/BPD diagnoses. All comparisons, except for *angry*, were robust to Bonferroni correction p=.025. These significant differences dissipated when models were adjusted for anxiety and depression (Model 2).

Table 5.3 Between-diagnoses differences on mood intensity as estimated by multilevel modelling

Intensity	Model parameters for group	ADHD diagnosis vs BPD diagnosis		ADHD diagnosis vs ADHD/BPD comorbid diagnosis		BPD diagnosis vs comorbid ADHD/BPD diagnosis	
		Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Happy	Estimate	15.75	6.12	14.99	2.55	-0.75	-3.58
	S.E	4.42	4.97	4.24	5.32	4.66	4.55
	p value	**.002**	1	**.002**	1	.872	1
Excited	Estimate	12.17	5.44	8.33	.42	-3.84	-5.02
	S.E	5	5.85	4.79	6.27	5.27	5.36
	p value	.068	1	.257	1	.816	1
Sad	Estimate	-18.82	-2.1	-15.52	5.86	3.30	7.96
	S.E	5.20	5.34	4.98	5.72	5.48	4.89
	p value	**.002**	1	**.007**	1	.549	.641
Irritable	Estimate	-8.72	-2.22	-11.41	-1.73	-2.69	.49
	S.E	4.61	5.31	4.41	5.69	4.85	4.86
	p value	.123	1	.034	1	.581	1
Angry	Estimate	-11.69	-3.48	-11.56	.11	.12	3.59
	S.E	4.66	5.3	4.46	5.68	4.91	4.85
	p value	.044	1	.044	1	.980	1

Model 1: Multilevel models unadjusted
Model 2: Multilevel models adjusted for BSI anxiety and depression scores

5.4.3.2 Instability

Multilevel models revealed a non-significant interaction effect of ADHD*BPD on all items, in unadjusted (Model 1) and adjusted (Model 2) models for depression and anxiety.

There were some differences between the control and BPD diagnosis (see Table 5.4), as well as controls and the comorbid ADHD/BPD diagnosis (Model 1) in the instability of positive and negative emotion items, of which only *sad* between controls and the BPD diagnosis, and all the negative emotion items between controls and comorbid ADHD/BPD diagnosis were robust to Bonferroni adjustment (p=.025). All significant differences dissipated when controlling for anxiety and depression (Model 2).

Post-hoc tests revealed no significant differences between controls and the ADHD diagnosis with and without controlling for depression and anxiety on the instability of *happy*, *excited*, and *angry*. The ADHD diagnosis reported significantly more

instability of *sad* and *irritable* compared to controls (Model 1). When models were adjusted for anxiety and depression, these significant differences dissipated (Model 2). Comparisons were robust to Bonferroni correction (p=.025).

Table 5.4 Differences between diagnostic groups and control group on mood instability as estimated by multilevel modelling

Instability	Model parameters for group	No diagnosis vs ADHD diagnosis		No diagnosis vs BPD diagnosis		No diagnosis vs comorbid ADHD/BPD diagnosis	
		Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Happy	Estimate	-.39	-.25	-.31	-.02	-.69	-.31
	S.E	.22	.25	.25	.36	.24	.4
	p value	.400	1	.638	1	.028	1
Excited	Estimate	-.29	-.27	.35	.11	-.14	-.38
	S.E	.28	.32	.31	.45	.3	.49
	p value	1	1	1	1	1	1
Sad	Estimate	-.96	-.69	-1.15	-.36	-1.38	-.44
	S.E	.30	.33	.33	.47	.32	.52
	p value	**.007**	.230	**.004**	1	**<.001**	1
Irritable	Estimate	-.13	-.95	-.12	-.71	-.17	-.87
	S.E	.04	.37	.05	.52	.05	.57
	p value	**.021**	.070	.055	.691	**.004**	.676
Angry	Estimate	-.12	-.68	-.20	-.37	-.26	-.5
	S.E	.07	.43	.07	.6	.07	.67
	p value	.251	.692	.050	1	**.003**	1

Model 1: Multilevel models unadjusted
Model 2: Multilevel models adjusted for BSI anxiety and depression scores

In the comparison of the clinical diagnoses of ADHD, BPD and comorbid ADHD/BPD, there were no differences in the instability of all positive and negative emotion items (see Table 5.5). Anxiety and depression had no effect in the instability models when comparing clinical diagnoses and the adjusted results are therefore not presented below.

Table 5.5 Between-diagnoses differences on mood instability as estimated by multilevel modelling

Instability	Model parameters for group	ADHD diagnosis vs BPD diagnosis	ADHD diagnosis vs ADHD/BPD comorbid diagnosis	BPD diagnosis vs comorbid ADHD/BPD diagnosis
Happy	Estimate S.E *p* value	.08 .25 .741	-.29 .24 .638	-.38 .26 .623
Excited	Estimate S.E *p* value	.64 .31 .270	.14 .30 1	-.50 .33 .680
Sad	Estimate S.E *p* value	-.19 .33 1	-.42 .32 .589	-.22 .35 1
Irritable	Estimate S.E *p* value	.01 .05 1	-.03 .05 1	-.04 .05 1
Angry	Estimate S.E *p* value	-.08 .07 .589	-.14 .07 .200	-.06 .07 .589

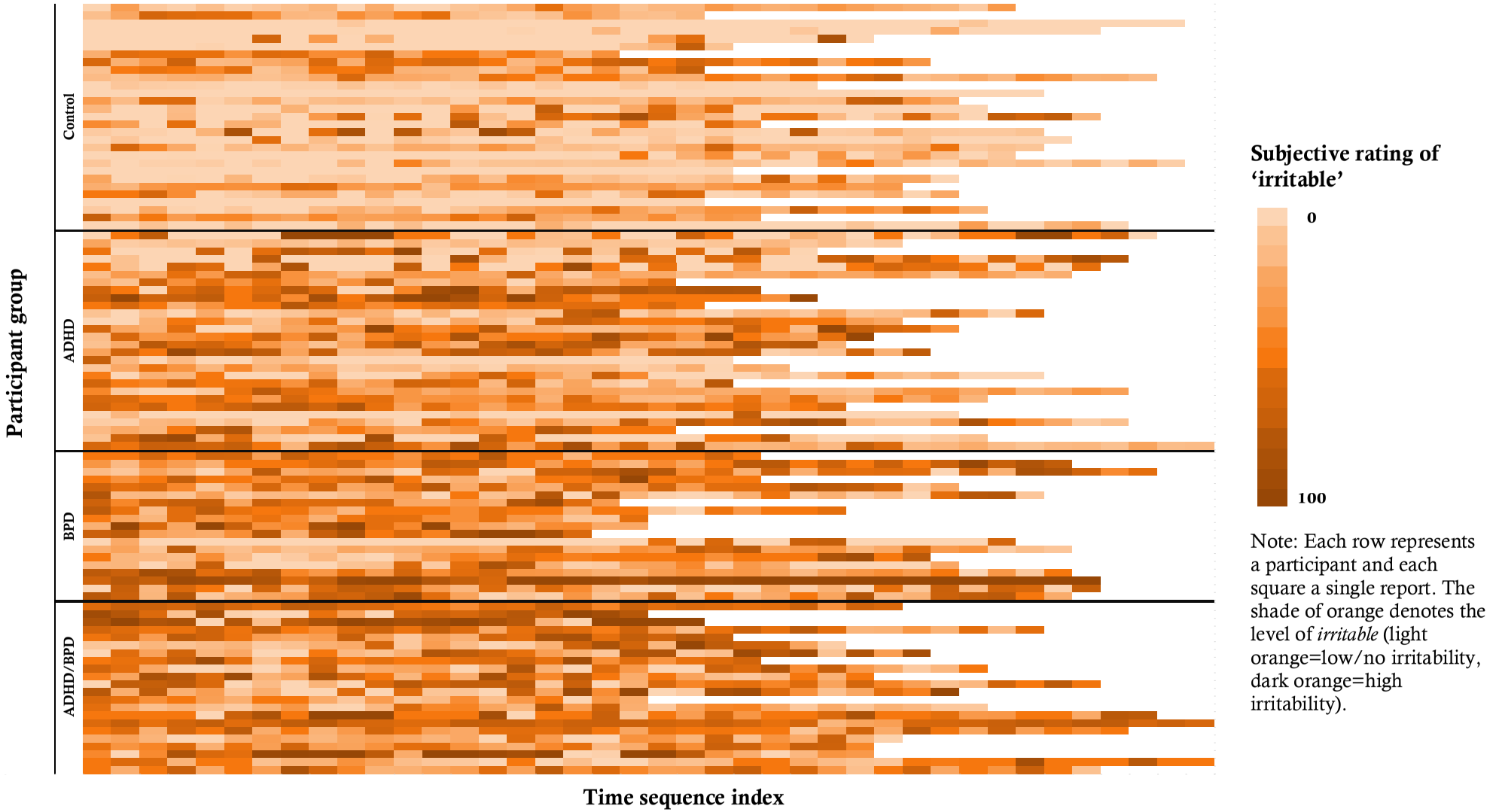
5.4.4 Visualising emotions

Figure 5.2 shows a 3-dimensional representation of the data (covering subject, time and intensity) for the emotion ratings of *irritable* over the 5-day ambulatory monitoring period. Each horizontal row represents a participant, each square corresponds to a single report and the colour shade denotes the level of irritability (with darker squares indicating higher ratings). Variability in the length of individual bars indicates differences in compliance. The frequency and fast changing intensity seen in the lower three portions of the figure represents the within-subject variability in individuals with ADHD, BPD and ADHD/BPD respectively, and the darker shade overall suggests a greater proportion of higher ratings of *irritable*.

The figure also illustrates differences in intra-individual variability within groups, with a few individuals with ADHD and BPD showing more similar patterns to those of controls, and a few controls showing more similar patterns to those seen in ADHD and BPD.

The heatmap reveals observable differences among the patient groups and healthy controls. All three patient groups showed higher intensity of *irritable* (i.e., more dark squares) and more changes over time (i.e., more colour changes across ratings) than healthy controls. However, the clinical groups cannot be distinguished from one another regarding the frequency of high *irritable* ratings (i.e., the number of dark squares) or changeability (i.e., the colour changes).

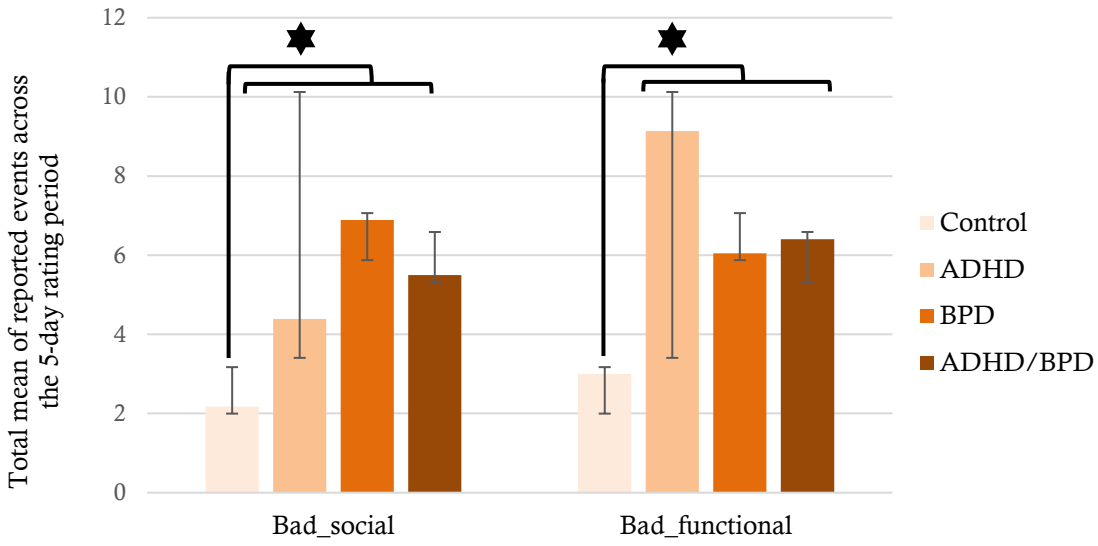
Figure 5.2 Heatmap of *irritable* ratings for the control and clinical groups



5.4.5 Bad social and functional events

Controls reported significantly less *bad social* and *bad functional* events compared to all three clinical groups (p<.05). The ADHD, BPD and comorbid ADHD/BPD groups did not differ significantly on the frequency of reported bad events (p>.05) (See Figure 5.3).

Figure 5.3 Frequency of bad events



The contribution of reported *bad social* and *bad functional* events in the intensity and instability of *sad*, *irritable* and *angry* were investigated below. First, multilevel models were run to investigate the relative contribution of bad events as predictors in the models, and secondly additional models were run to investigate the interaction of diagnosis (ADHD and BPD) and bad events on emotions.

Main effects from the multilevel models indicated that across the whole sample, *bad social* and *bad functional* events both have a significant main effect on the intensity and instability of negative emotion items (sad, irritable and angry; p<.001).

Results also showed that after the inclusion of *bad social* (Model 3) and *bad functional* (Model 4) events in the multilevel models of intensity and instability of emotions, despite the small changes in the estimates of the models, a similar pattern of results

was seen as in the models without these predictors (See Tables 5.6 and 5.7 for *bad social* events, and Tables 5.8 and 5.9 for *bad functional* events).

Table 5.6 Between-diagnoses differences on the effect of bad social events on mood intensity

Intensity	Model parameters for group	ADHD diagnosis vs BPD diagnosis			ADHD diagnosis vs ADHD/BPD comorbid diagnosis			BPD diagnosis vs comorbid ADHD/BPD diagnosis		
		Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Sad	Estimate	-18.82	-2.1	-1.87	-15.52	5.86	5.50	3.30	7.96	7.37
	S.E	5.20	5.34	5.28	4.98	5.72	5.66	5.48	4.89	4.84
	p value	**.002**	1	1	**.007**	1	1	.549	.641	.786
Irritable	Estimate	-8.72	-2.22	-1.75	-11.41	-1.73	-2.45	-2.69	.49	-.70
	S.E	4.61	5.31	5.10	4.41	5.69	5.46	4.85	4.86	4.67
	p value	.123	1	1	.034	1	1	.581	1	1
Angry	Estimate	-11.69	-3.48	-3.03	-11.56	.11	-.58	.12	3.59	2.45
	S.E	4.66	5.3	5.09	4.46	5.68	5.46	4.91	4.85	4.67
	p value	.044	1	1	.044	1	1	.980	1	1

Model 1: Multilevel models unadjusted
Model 2: Multilevel models adjusted for depression, anxiety
Model 3: Multilevel models adjusted for depression, anxiety and bad social events

Table 5.7 Between-diagnoses differences on the effect of bad social events on mood instability

Instability	Model parameters for group	ADHD diagnosis vs BPD diagnosis			ADHD diagnosis vs ADHD/BPD comorbid diagnosis			BPD diagnosis vs comorbid ADHD/BPD diagnosis		
		Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Sad	Estimate	-18.82	-2.1	.31	-15.52	5.86	.22	3.30	7.96	-.09
	S.E	5.20	5.34	.39	4.98	5.72	.42	5.48	4.89	.36
	p value	**.002**	1	1	**.007**	1	1	.549	.641	1
Irritable	Estimate	-8.72	-2.22	.04	-11.41	-1.73	.01	-2.69	.49	-.03
	S.E	4.61	5.31	.06	4.41	5.69	.06	4.85	4.86	.05
	p value	.123	1	1	.034	1	1	.581	1	1
Angry	Estimate	-11.69	-3.48	.01	-11.56	.11	-.02	.12	3.59	-.02
	S.E	4.66	5.3	.08	4.46	5.68	.09	4.91	4.85	.08
	p value	.044	1	1	.044	1	1	.980	1	1

Model 1: Multilevel models unadjusted
Model 2: Multilevel models adjusted for depression, anxiety
Model 3: Multilevel models adjusted for depression, anxiety and bad social events

Table 5.8 Between-diagnoses differences on the effect of bad functional events on mood intensity

Intensity	Model parameters for group	ADHD diagnosis vs BPD diagnosis			ADHD diagnosis vs ADHD/BPD comorbid diagnosis			BPD diagnosis vs comorbid ADHD/BPD diagnosis		
		Model 1	Model 2	Model 4	Model 1	Model 2	Model 4	Model 1	Model 2	Model 4
Sad	Estimate	-18.82	-2.1	-3.06	-15.52	5.86	4.45	3.30	7.96	7.51
	S.E	5.20	5.34	5.32	4.98	5.72	5.70	5.48	4.89	4.87
	p value	**.002**	1	1	**.007**	1	1	.549	.641	.76
Irritable	Estimate	-8.72	-2.22	-3.69	-11.41	-1.73	-3.87	-2.69	.49	-.18
	S.E	4.61	5.31	5.28	4.41	5.69	5.66	4.85	4.86	4.84
	p value	.123	1	1	.034	1	1	.581	1	1
Angry	Estimate	-11.69	-3.48	-4.76	-11.56	.11	-1.75	.12	3.59	3.01
	S.E	4.66	5.3	5.26	4.46	5.68	5.64	4.91	4.85	4.82
	p value	.044	1	1	.044	1	1	.980	1	1

Model 1: Multilevel models unadjusted
Model 2: Multilevel models adjusted for depression, anxiety
Model 4: Multilevel models adjusted for depression, anxiety and bad functional events

Table 5.9 Between-diagnoses differences on the effect of bad functional events on mood instability

Instability	Model parameters for group	ADHD diagnosis vs BPD diagnosis			ADHD diagnosis vs ADHD/BPD comorbid diagnosis			BPD diagnosis vs comorbid ADHD/BPD diagnosis		
		Model 1	Model 2	Model 4	Model 1	Model 2	Model 4	Model 1	Model 2	Model 4
Sad	Estimate	-18.82	-2.1	.28	-15.52	5.86	.12	3.30	7.96	-.16
	S.E	5.20	5.34	.38	4.98	5.72	.41	5.48	4.89	.35
	p value	**.002**	1	1	**.007**	1	1	.549	.641	1
Irritable	Estimate	-8.72	-2.22	.16	-11.41	-1.73	-.06	-2.69	.49	-.22
	S.E	4.61	5.31	.43	4.41	5.69	.46	4.85	4.86	.39
	p value	.123	1	1	.034	1	1	.581	1	1
Angry	Estimate	-11.69	-3.48	.21	-11.56	.11	.03	.12	3.59	-.18
	S.E	4.66	5.3	.49	4.46	5.68	.53	4.91	4.85	.45
	p value	.044	1	1	.044	1	1	.980	1	1

Model 1: Multilevel models unadjusted
Model 2: Multilevel models adjusted for depression, anxiety
Model 4: Multilevel models adjusted for depression, anxiety and bad functional events

Further models investigating the impact of diagnosis on the interaction of bad events on mood revealed that diagnosis does not have a significant effect ($p>.05$) on the impact of *bad functional* events on the intensity of *sad* and *irritable*, when comparing ADHD and BPD diagnoses. On the other hand, diagnosis had a significant effect on how *bad functional* events impacted intensity of *angry*, whereby

the BPD diagnosis reported higher intensity of *angry* than the ADHD diagnosis (p=.003). Results were similar in models controlling for anxiety and depression symptoms.

Regarding *bad social* events, diagnosis had no significant effect on the impact of *bad social* events on the intensity of *sad* and *angry*, when comparing ADHD and BPD diagnoses. While a significant effect of diagnosis on the event-by-*irritable* interaction was seen, whereby the ADHD diagnosis reported higher intensity of *irritable* than the BPD diagnosis (p=.010). When controlling for depression and anxiety symptoms, findings are similar for *sad* and *angry,* and a more robust significance value is depicted for *irritable* (p=.001).

Diagnosis-by-event interaction models on the instability of negative emotions items were all non-significant.

5.4.6 Relationship of experience sampling data and retrospective measures of emotional dysregulation

Bivariate correlations between total mean scores obtained from the ALS and WRAADDS-EDS and mean ratings of mood instability (i.e. MSSD) from ESM assessments confirmed significant small to moderate associations between the two types of measures across the whole sample (see Table 5.10). Correlations became non-significant when investigated in the control participants and the clinical cases separately. This most likely reflects the generally lower levels of reported emotional dysregulation in both the retrospective and ambulatory monitoring measures in the control group, and the higher levels in the clinical groups, leading to less variation in the data when investigated in the groups separately, as opposed to the investigation across the whole sample.

Table 5.10 Correlation coefficients for relationship between retrospective measures and mean instability from ESM data of emotional dysregulation across the whole sample

MSSD	ALS	WRAADDS-EDS
Happy	.36*	.33*
Excited	.18	.17
Sad	.37*	.37*
Irritable	.30*	.33*
Angry	.46*	.50*

Correlation is significant at the .01 level (2-tailed).

5.4.7 Relationship between BSI scores of depression and anxiety and measures of emotion instability

Given the significant effect of depression and anxiety symptoms in measures of emotion instability, Table 5.11 shows the correlations between BSI scores of depression and anxiety, retrospective and ESM measures of emotion instability. Apart from instability of *excited*, retrospective and ESM measures of emotion instability show moderate to strong correlations with BSI scores of anxiety and depression.

Table 5.11 Correlation coefficients for relationships between MSSDs and retrospective measures of emotion instability with BSI scores of depression and anxiety across the whole sample

MSSD	BSI_Depression	BSI_Anxiety
Happy	.28*	.29*
Excited	.02	.08
Sad	.40*	.41*
Irritable	.33*	.37*
Angry	.52*	.57*
ALS	.65*	.76*
WRAADDS-EDS	.68*	.76*

Correlation is significant at the .01 level (2-tailed).

5.5 Discussion

The main aim of this study was to assess the similarities and differences in measures of emotional dysregulation in adults with ADHD, BPD, comorbid ADHD/BPD and controls using ambulatory monitoring and retrospective questionnaire measures.

5.5.1 The dynamic changes of emotions

Regarding retrospective questionnaire measures, the clinical diagnoses reported significantly heightened levels of emotional dysregulation compared to controls, yet no distinctive differences were detected between the diagnoses on these measures.

Regarding ESM measures of emotional dysregulation, the BPD and comorbid ADHD/BPD diagnoses displayed differences in the intensity and instability of positive and negative emotion items compared to controls. Consistent with these findings, the ADHD diagnosis showed heightened intensity and instability of *sad* and *irritable* compared to controls.

On the other hand, no differences were seen between the ADHD diagnosis and controls on the intensity and instability of positive emotion items and *angry*. This suggested that emotions of *happy*, *excited* and *angry* are similarly expressed in controls and ADHD. The findings supported the clinical descriptions in the literature of emotional dysregulation in these clinical populations, including "definite shifts from normal mood to depression or mild excitement" (Reimherr et al., 2005, p.125), and "rapid shifts into depression and excitability" (Asherson, Chen, Craddock, & Taylor, 2007, p.7) in ADHD, and "rapid changes in mood" (Carpenter & Trull, 2013, p.3), and "high levels of negative affect, lower levels of positive affect, and more instability if negative affect" (Trull, 2018, p.2) in BPD.

Finally, results from the models investigating differences in the intensity of emotions between the clinical diagnoses indicated some differences with ADHD showing less intensity of negative emotions than BPD. No differences in the instability of positive and negative emotions were seen between the clinical diagnoses.

All the above-mentioned significant case-control differences, as well as differences seen between the ADHD and BPD diagnoses were accounted for by symptoms of anxiety and depression of the BSI.

Overall, findings of this study suggest that intensity and instability of positive emotions are not able to distinguish between individuals with ADHD and controls, contrary to clear differences between controls and BPD populations. Additionally, emotional dysregulation cannot seem to distinguish between ADHD and BPD. Anxiety and depression seem to be strongly associated with intensity and instability of emotions in ADHD and BPD, potentially being markers of this dynamic phenomenon.

5.5.2 Bad events

ADHD and BPD have both been associated with greater adversity and acute stressful situations in everyday life (Bourvis, Aouidad, Cabelguen, Cohen, & Xavier, 2017; van der Meer et al., 2014), which raises the question whether emotional dysregulation is simply a reaction to the greater number of adverse situations in daily life and whether emotional dysregulation in ADHD and BPD differ by the type of adverse events (*functional* versus *social*).

Overall, all three clinical diagnoses reported a higher number of bad events compared to controls, whilst not differing between each other.

Both bad social and bad functional events had a significant effect on the intensity and instability of negative emotions, yet covariation for the effect of these bad events did not eliminate or generate any group differences. The models controlling for these bad events only slightly changed still reflecting the same pattern of results of that seen without the covariate. In line with the findings in adult males with ADHD of Skirrrow et al. (2014), this could indicate that heightened intensity and instability of negative affect has both a reactive and an endogenously driven component in both ADHD and BPD, and differences between the groups are not accounted for by differences in the frequency of reported bad events. Similar findings in depression have *shown* that although reactions to significant

external events contribute to emotional instability, they do not fully explain the levels of emotional instability in major depressive disorder (Thompson et al., 2012).

Regarding differences between ADHD and BPD on the type of bad events, for most of the emotions the type of event (social or functional) had the same effect for both ADHD and BPD diagnoses. The exceptions were that the ADHD diagnosis reported higher intensity of *irritable* in the presence of *bad social* events, whilst the BPD diagnosis reported higher intensity of *angry* in the presence of *bad functional* events. These two isolated findings were not however expected, are hard to explain, and should therefore be treated with caution.

Overall, the findings on bad events do not support the initial hypothesis of emotional dysregulation being triggered more frequently by *bad social* events in BPD, as opposed to *bad functional* events in ADHD, overall indicating that type of events doesn't distinguish the disorders. This could be due to the pseudorandomised sampling strategy of the ESM data which may not have been adequate to investigate the effects of adverse life events on negative emotions. An event-contingent paradigm in future research, where reports are provided when experiencing certain environmental events, as opposed to predefined schedule, could be more appropriate to test the reactivity model of emotional dysregulation (Trull et al., 2008).

5.5.3 Relationship between retrospective questionnaires and prospective ambulatory monitoring

The limited association as shown by the relatively low correlations between the questionnaire measures and ambulatory assessment measures of emotional dysregulation across the control and clinical samples together, suggests only a small to moderate concordance between these two types of measures. These findings are in line with previous research in ADHD (Skirrow et al., 2014), bulimia nervosa (Anestis et al., 2010) and personality disorders (Solhan et al., 2009), where weak associations in such comparisons were also seen. Given the dynamic nature of emotions on one hand, and the recall bias associated with retrospective measures on the other hand, overall, these results indicated that whilst these measures can be considered complementary, they may not be considered equivalent.

5.5.4 Strengths and limitations

This study was the first to compare ADHD and BPD for measures of emotional dysregulation using a prospective ESM approach, with high sampling frequency and time-sensitive instability indices (Santangelo et al., 2014). Despite using multiple measures of emotional dysregulation and including carefully selected and diagnosed clinical cases, the findings should be considered in light of several limitations.

The moderate compliance rate obtained in this study was low compared to previous studies in BPD and depression, with rates around 90% and above (Ebner-Priemer, Welch, et al., 2007; Solhan et al., 2009), yet was more closely in line with other ESM studies in outpatients with schizophrenia (69%; Granholm, Loh, & Swendsen, 2008), adult men with ADHD (64%; Skirrow et al., 2014), and healthy adolescents (71%; Hedeker, Mermelstein, Berbaum, & Campbell, 2009).

Additional limitations concern the general sample demographics. Results may not be generalised beyond the specific demographic and diagnostic groups utilised in this study, which included only females from outpatient ADHD and BPD specialist clinics. Yet, this had the advantage of not accounting for potential sex differences in the analyses. Results from the comparisons between the ADHD diagnosis and controls were similar with the findings of Skirrow et al. (2014) in adult men with ADHD and without other comorbidities, who showed increased instability of *irritable* and *angry* and no differences in the intensity and instability of positive emotions compared to controls. On the other hand, to the best of my knowledge, no studies of ESM have been conducted in males with BPD. Two ESM studies in BPD initially recruited six (Jahng et al., 2011) and two (Russel et al. 2007) males respectively into their samples, but subsequently had to exclude them from analyses, as the number was not sufficient for the examination of sex differences. Therefore, future studies are required to confirm the findings reported here in males with BPD.

In this study, care was taken to exclude individuals with comorbid major depressive disorders and anxiety disorders. Yet, all three clinical groups showed equally heightened symptoms of depression and anxiety compared to controls, and

significant differences between diagnoses in measures of emotional dysregulation were all accounted for by these depressive and anxious symptomatology. Emotional dysregulation seems to have a similar relationship to depression and anxiety in both ADHD and BPD, further suggesting that the type of emotional dysregulation is similar in the two disorders. Therefore, it seems plausible that anxious and depressive symptoms have a marked effect on emotional dysregulation, and their close association with intensity and instability of emotional dysregulation could mean that they might all reflect a single underlying construct. This was in line with the findings of Skirrow at al. (2014), where comorbid depression and anxiety disorders were systematically excluded in men with ADHD, yet high subthreshold depressive symptoms were present in the sample, and comparable results to this study of emotional intensity and instability were seen. Of note, the depression and anxiety subscales of the BSI have been shown to have good predictive ability for DSM-IV diagnoses of depression and anxiety (Petkus et al., 2009), yet were recommended not to be relied upon as an alternative to diagnosis (Recklitis, Blackmon, & Chang, 2017). Future studies should address the underlying mechanisms of depression and anxiety, how they relate to emotional dysregulation and their potential implications on treatment outcome.

The nature of self-reported assessments in all measures used in this study should be considered when interpreting the results. Whether retrospectively assessed in questionnaire measures, or prospectively in ESM measures, reports were based on the subjective view of the individuals of their affective states. Additionally, it will remain unknown whether the extreme mood changes were triggered by the reported bad events, or whether they were over-reported and influenced by these bad events. Future investigations of ADHD and BPD using ESM approach could additionally incorporate more objective physiological measures (e.g. heart rate, breathing, arousal), which will reflect emotional reactivity and instability more accurately (Alpers, 2009), and/or employ more complex network analyses, which is an empirical approach when investigating interactive components (Bringmann et al., 2016; Hasmi et al., 2017).

5.5.5 Conclusions

The current study employed ambulatory assessments to qualitatively characterise the intensity and instability in emotions experienced by adult females with ADHD and BPD over a period of five days. Real-life assessments of emotions showed complementary findings to data of retrospectively reported emotional dysregulation. The lack of specificity in the intensity and instability of negative affect in ADHD and BPD was not entirely surprising, and were line with unspecific patterns of emotional dysregulation also reported in bulimia nervosa, posttraumatic stress disorder, depression, anxiety disorders and bipolar disorder (Santangelo et al., 2014). Notably, differences in intensity and instability of mood could not be accounted for by the presence and impact of bad negative events in ADHD or BPD.

Despite the fact that BPD is the only disorder where emotional dysregulation is a diagnostic criterion, results in this study showed similar patterns of heightened instability in ADHD as well. Findings further support the notion that emotional dysregulation is a transdiagnostic clinical symptom of several psychiatric conditions and could not be used to distinguish between disorders.

Promising avenues for future research include to statistically model the dynamic interplay between affect and self-esteem to discriminate between transdiagnostic and disorder-specific mechanisms as previous findings have shown that individuals with unstable self-esteem could be more reactive to daily events (Greenier et al., 1999; Meier, Semmer, & Hupfeld, 2009). Additional suggestions by the Research Domain Criteria (RDoC; Insel et al., 2010) are to explore overlapping underlying mechanisms of emotional dysregulation using dimensions of neurobiology and observable behaviour (integrated information from genomics and circuits to behaviour and self-reports).

Chapter 6: Effects of stimulants and atomoxetine on emotional lability in adults: A systematic review and meta-analysis

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Review

Effects of stimulants and atomoxetine on emotional lability in adults: A systematic review and meta-analysis

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ABSTRACT

Background: Emotional lability (EL) is an associated feature of attention-deficit/hyperactivity disorder (ADHD) in adults, contributing to functional impairment. Yet the effect of pharmacological treatments for ADHD on EL symptoms is unknown. We conducted a systematic review and meta-analysis to examine the effects of stimulants and atomoxetine on symptoms of EL and compare these with the effects on core ADHD symptoms.

Methods: A systematic search was conducted on the databases Embase, PsychInfo, and Ovid Medline® and the clinicaltrials.gov website. We included randomised, double-blind, placebo-controlled trials of stimulants and atomoxetine in adults aged 18–60 years, with any mental health diagnosis characterised by emotional or mood instability, with at least one outcome measure of EL. All identified trials were on adults with ADHD. A random-effects meta-analysis with standardised mean difference and 95% confidence intervals was used to investigate the effect size on EL and compare this to the effect on core ADHD symptoms.

Results: Of the 3,864 publications identified, nine trials met the inclusion criteria for the meta-analysis. Stimulants and atomoxetine led to large mean weighted effect-sizes for on ADHD symptoms ($n = 9$, SMD = −0.8, 95% CI: −1.07 to −0.53). EL outcomes showed more moderate but definite effects ($n = 9$, SMD = −0.41, 95% CI: −0.57 to −0.25).

Conclusions: In this meta-analysis, stimulants and atomoxetine were moderately effective for EL symptoms, while effect size on core ADHD symptoms was twice as large. Methodological issues may partially explain the difference in effect size. Reduced average effect size could also reflect heterogeneity of EL with ADHD pharmacotherapy responsive and non-responsive sub-types. Our findings indicate that EL may be less responsive than ADHD symptoms overall, perhaps indicating the need for adjunctive psychotherapy in some cases. To clarify these questions, our findings need replication in studies selecting subjects for high EL and targeting EL as the primary outcome.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental condition affecting around 5% of children [1]. Longitudinal follow-up studies show that ADHD frequently persists into adulthood, either as the full blown disorder, or as persistent subthreshold levels of symptoms causing impairment [2,3], with epidemiological surveys suggesting an estimated prevalence in adults of around 3–4% [4]. Although inattention, hyperactivity and impulsivity are considered to be the core symptoms of ADHD [5], emotional lability (EL), characterised by low frustration tolerance, irritability and mood lability, is a commonly associated feature that causes considerable distress to individuals and their families [6]. Clinically significant levels of EL are present in around 70–90% of adults with ADHD, and is an independent predictor of functional impairments beyond those accounted for by inattention and hyperactivity-impulsivity [7–10].

The importance of EL in adult ADHD was established by Wood, Wender and colleagues, who were among the first to describe the syndrome and included affective lability, hot temper, and stress intolerance as core symptoms of the disorder [11,12]. The current diagnostic and statistical manual of mental disorders (DSM-5) describes such emotional symptoms as associated features of ADHD that support the diagnosis [13]. Furthermore, high levels of EL are also observed in ADHD patients who do not present with co-occurring mental health disorders [7], indicating that the association

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of EL with ADHD cannot always be accounted for by the presence of comorbid disorders such as bipolar or borderline personality disorders [14].

Debate as to whether EL reflects a core domain of ADHD in adults is ongoing [5,15,16]. In particular it is unclear whether medications such as stimulants and atomoxetine, used in the treatment of ADHD, also lead to reductions in EL. Randomized placebo controlled trials in adults with ADHD conclusively show that both groups of medications lead to clinically significant reductions in symptoms of ADHD symptoms [9,17–20]. However, the effects of drugs used to treat ADHD on EL are yet to be established.

In order to assess the effects of stimulants and atomoxetine on EL in adults we conducted a systematic review and meta-analysis of randomised placebo-controlled trials. Our primary aim was to quantify the effects of stimulants and atomoxetine on EL. Our secondary aim was to contrast the effects of stimulants and atomoxetine on EL with the effects on the core ADHD symptoms of inattention and hyperactivity-impulsivity in the same studies.

Table 1
Search strategy.

Database	Search Strategy
Ovid Medline (1946 to June week 1, 2015) Embase (1974 to June 10, 2015) PsychInfo (1806 to June week 2, 2015)	Key Word search: (“affect*” or “oppositional” or “conduct” or “aggression” or “mood” or “emotion*” or “instability” or “lability” or “*regulation” or “bipolar”) and (“stimulants” or “*methylphenidate*” or “*amphetamine*” or “*amfetamine*” or “atomoxetine”) and (“RCT” or “randomized controlled trial” or “randomised controlled trial” or “double blind study” or “clinical trial” or “placebo controlled”)
Clinicaltrials.gov	(“affect*” OR “oppositional” OR “conduct” OR “aggression” OR “mood” OR “emotion*” OR “instability” OR “lability” OR “*regulation” OR “bipolar”) AND (“stimulants” OR “*methylphenidate*” OR “*amphetamine*” OR “*amfetamine*” OR “atomoxetine”)

2. Methods

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21].

2.1. Search strategy and selection criteria

Studies were included if: (a) they were randomised double-blind placebo-controlled trials of stimulants or atomoxetine; (b) participants were adults aged 18–60 years with any mental health diagnosis associated with EL[1]; (c) the study measured at least one outcome of behavioural change related to EL; (d) for each outcome measure, mean (M) and standard deviation (SD) from baseline and follow-up for the placebo and active group were reported or obtained upon contacting the authors. Trials published in languages other than English were excluded for feasibility reasons of translation.

A literature search was conducted using pre-specified search terms (Table 1) using the following databases: Embase (1974 to 2015 June 10th), PsychInfo (1806 to June week 2, 2015) and Ovid Medline® (1946 to June week 1, 2015). Unpublished or ongoing trials were searched on the clinicaltrials.gov website. Authors were contacted to request missing data.

In spite of the official systematic search being stopped in June 2015, there were no new clinical trials published meeting the selection criteria of this systematic review up until 2nd May, 2017.

To assess for the risk of bias, study quality was assessed by two independent authors (TRM & PM) according to PRISMA guidelines and the Cochrane Handbook of Systematic Reviews [22] (Tables 2 and 3). TRM and PM then met to discuss assessments and reach a consensus on study inclusion. Unresolved classification of studies was arbitrated by PA and REC. Studies were classified overall as unclear, low or high risk. High risk studies were excluded.

Data extraction was performed by TRM and checked by two research assistants. The main outcome measures were raw scores of mean and standard deviation of the pre- and post-treatment measures of EL and DSM-IV ADHD symptoms for active and placebo arms. Intent to treat analysis (ITT) was reported. For trials with a cross-over design, only the initial pre-cross-over data was included, if available, and treated as a parallel group trial. We used this rather conservative approach because there was lack of sufficient data to permit analysis of within-individual change (i.e. correlations of scores between conditions were not given). Missing data that remained unavailable after contacting authors were not imputed.

2.2. Outcome measures

Two outcome domains were included in the meta-analysis: EL and DSM-IV ADHD symptoms. EL was measured using the emotion dysregulation subscale of the Wender Reimherr Adult Attention Deficit Disorder Scale (WRAADDS-EDS) [11], which combined subscales of hot temper, affective lability and emotional over-reactivity, or the emotion control subscale of the Behaviour Rating Inventory of Executive Function (BRIEF-A) [23]. ADHD DSM-IV domains were measured by the investigator-rated, self-rated or informant-rated Conners Adult ADHD Rating Scale (CAARS) [24], ADHD- Rating Scale (ADHD-RS) or the investigator rated WRAADDS [11]. Table 4 contains a detailed list of measures used in these two domains.

2.3. Data analysis

2.3.1. Statistical analyses

Analyses were performed in STATA 11.2 [25]. An initial analysis in the full sample across the two domains of EL and ADHD symptoms was run, following this, subgroup analyses (see below) were conducted.

We report the SMD calculated as the mean pre-to-post-treatment change, minus the mean pre-to-post-placebo group change, divided by the pooled pre-test standard deviation (SD), with a bias adjustment. The equation for this method is presented below [26]. Effects sizes were classified according to Cohen's d as follow: d = 0.2, d = 0.5 and d = 0.8 as small, medium and large respectively [27].

$$d_{ppc2} = C_P\left[\frac{(M_{post,T}-M_{pre,T})-(M_{post,C}-M_{pre,C})}{SD_{pre}}\right]$$

$$SD_{pre} = \sqrt{\frac{(n_T-1)SD^2_{pre,T}+(n_C-1)SD^2_{pre,C}}{n_T+n_C-2}}$$

$$C_P = 1-\frac{3}{4(n_T+n_c-2)-1}$$

[1] ADHD was not specified as a search term, with the intention of including trials of stimulants and atomoxetine on EL in non-ADHD populations. However, all resulting trials were conducted on adults with ADHD.

Table 2
Study quality appraisal (scored as low, high or unclear risk).

First Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk	Other limitations
Reimherr et al. (2007)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	N/A	Unclear	No
Wender et al. (2011)	Low	Unclear	Low	Low	Low	Low	N/A	Unclear	No
Reimherr et al. (2005)	Unclear	Unclear	Unclear	Low	Low	Low	N/A	Unclear	No
Adler et al. (2013)	Unclear	Low	Low	Unclear	Low	Low	N/A	Unclear	No
Adler et al. (2014)	Low	Low	Low	Unclear	Low	Low	Low	Unclear	No
Rosler et al. (2010)	Unclear	Unclear	Unclear	Unclear	Low	Low	N/A	Unclear	No
Marchant et al. (2011)	Low	Unclear	Unclear	Unclear	Unclear	Low	N/A	Unclear	No
Goto et al. (2011)	Unclear	Unclear	Unclear	Unclear	Low	Low	N/A	Unclear	No
Retz et al. (2012)	Low	Unclear	Unclear	Unclear	Low	Low	N/A	Unclear	No

Table 3
Study quality appraisal.

First Author	Reason if not low risk?	Other limitations
Reimherr et al. (2007)	Random sequence generation: Insufficient information Allocation concealment: Insufficient information Blinding of participants and personnel: Procedure unspecified Blinding of outcome: Procedure unspecified Incomplete outcome data: 6 drop-outs, reasons not stated	N/A
Wender et al. (2011)	Allocation concealment: Insufficient information	N/A
Reimherr et al. (2005)	Random sequence generation: Insufficient information Allocation concealment: Unspecified Blinding participants and personnel: Insufficient information	N/A
Adler et al. (2013)	Random sequence generation: Unspecified Blinding of outcome assessment: Unspecified	N/A
Adler et al. (2014)	Blinding of outcome assessment: Insufficient information	N/A
Rosler et al. (2010)	Random sequence generation: Randomised Allocation concealment: Insufficient information Blinding of participants: Double-blind Blinding of outcome assessment: Insufficient information.	N/A
Merchant et al. (2011)	Allocation concealment: Unspecified Blinding of participants and personnel: Unspecified Binding of outcome assessment: Unspecified Incomplete outcome data: High drop-out rate with no explanations	N/A
Goto et al. (2011)	Random sequence generation: Unspecified Allocation concealment: Unspecified Blinding of participants and personnel: Insufficient information. Blinding of outcome assessment: Unspecified	N/A
Retz et al. (2012)	Allocation concealment: Insufficient information Blinding of participants and personnel: Unspecified Binding of outcome assessment: Unspecified	N/A

Note. d_{ppc2}: standardised mean difference (SMD); C_p: bias adjustment; M: mean; T: treatment, C: control, Post: post-treatment, Pre: pre-treatment, SD: standard deviation, *n*: number of participants.

Given the between-study heterogeneity in terms of study design, trial duration, outcome measures and participant characteristics we chose *apriori* to use random-effects models [28]. A nominal level of significance was set at $P < .05$. The I^2 statistic assessed heterogeneity between studies. Publication bias was investigated on the basis of funnel plots using Begg & Mazumdar's rank correlation approach and the Egger regression asymmetry test.

2.3.2. Subgroup analyses

Additional analyses were conducted in subsets of the total sample to investigate the stability of the results to the scale used to measure EL (WRAADS-EDS versus BRIEF-A) and the class of study medication (stimulants versus atomoxetine).

Outcome measure: EL was measured by either BRIEF-A the emotion control subscale [23] or the WRAADDS-EDS [11]. Analyses were performed separately on the trials using the BRIEF-A ($n = 3$) and WRAADDS-EDS ($n = 6$).

Medication class: Included trials medicated participants with either stimulants or atomoxetine. Analyses were conducted separately on studies which used stimulants ($n = 6$) and atomoxetine ($n = 3$).

Medication class and outcome measure: To check whether the medication gave different effect size estimates when controlling for the EL scale (BRIEF-A or WRAADDS-EDS) used: we compared the effects of stimulants set against atomoxetine, first when EL was measured by the WRAADDS-EDS and then when it was measured by the BRIEF-A.

Table 4
Detailed breakdown of behavioural rating scales included in the meta-analysis per study by the two outcome measures.

First author	Domain(s) investigated	Rating scale	Measure included in meta-analysis[a]	Numbers in Analysis in FU	
				Active	Placebo
Reimherr et al. (2007)	Emotional lability	WRAADDS-EDS	Emotional lability	20	20
	ADHD symptoms	ADHD-RS	ADHD DSM-IV domains	20	20
Wender et al. (2011)	Emotional lability	WRAADDS-EDS	Emotional lability	58	57
	ADHD symptoms	WRAADDS	ADHD DSM-IV domains	58	57
Reimherr et al. (2005)	Emotional lability	WRAADDS-EDS	Emotional lability	225	226
	ADHD symptoms	CAARS- Investigator rated	ADHD DSM-IV domains	225	226
Adler et al. (2013)	Emotional control	BRIEF-A (BRI-emotional control subscale)-self-report	Emotional lability	79	75
	ADHD symptoms	CAARS- Informant rated	ADHD DSM-IV domains	79	80
Adler et al. (2014)	Emotional control	BRIEF-A (BRI-emotional control subscale)	Emotional lability	161	167
	ADHD symptoms	CAARS- Investigator rated	ADHD DSM-IV domains	192	199
Rösler et al. (2010)	Emotional lability	WRAADDS-EDS	Emotional lability	241	118
	ADHD symptoms	CAARS- Self report	ADHD DSM-IV domains	239	118
Marchant et al. (2011)	Emotional lability	WRAADDS-EDS	Emotional lability	26	33
	ADHD symptoms	CAARS- Investigator rated	ADHD DSM-IV domains	26	33
Goto et al. (2011)	Emotional control	BRIEF-A (BRI-emotional control subscale)-self-report	Emotional lability	178	190
	ADHD symptoms	CAARS- Investigator rated	ADHD DSM-IV domains	191	195
Retz et al. (2012)	Emotional lability	WRAADDS-EDS	Emotional lability	84	78
	ADHD symptoms	CAARS- Self report	ADHD DSM-IV domains	83	76

Note. BRIEF-A (BRI) = Behaviour Rating Inventory of Executive Function, behavioural regulation scales (Roth et al., 1996); WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale (Wender, 1995); CAARS = Conners' Adult ADHD Rating Scale (Conners, 1998); ADHD-RS = ADHD- Rating Scale

3. Results

3.1. Selection of studies

The initial database search identified 3864 unique publications. 403 abstracts were screened against the inclusion criteria, of which 385 were excluded because: the data were already used or reported in another publication ($n = 18$); the outcomes were unsuitable ($n = 44$); the studies were not randomised controlled trials ($n = 61$), failed to report a placebo group ($n = 4$); were open label trials ($n = 5$); used unsuitable medication (medications other than stimulants or atomoxetine) ($n = 14$) or population ($n = 6$); were not published in English ($n = 5$); requests for data from unpublished trials were not returned successfully ($n = 24$); or the trial was conducted on children ($n = 204$). Eighteen full-text articles were subsequently quality appraised and eight were excluded because of: an open label design ($n = 1$), unsuitable population ($n = 2$), unsuitable design ($n = 2$) and unsuitable outcome ($n = 3$). Ten studies met the inclusion criteria, but one of these had to be excluded on the grounds of missing statistics, leaving nine studies for inclusion in the final pool for the meta-analysis (Fig. 1 and Tables 5–7).

3.2. Quality and characteristics of studies included in qualitative synthesis

Nine studies were judged to be of sufficient quality and suitability to be included in the quantitative synthesis (Tables 2 and 3). Randomisation and allocation concealment were explicitly described in only one study [29]. In the remainders, this was absent or unclear. Means of blinding the participants, personnel and outcome assessment were unclear in seven studies, and were only clearly stated in three studies. In one study, 25.5% of the initially recruited participants dropped out prior to randomisation and another 12% following randomisation [19], and in another study, four subjects were eliminated after randomisation [30], raising concerns about the likelihood of selection bias. Study characteristics are outlined in Table 5.

3.3. Quantitative meta-analysis

Main effects from the meta-analysis of the nine included studies are summarised in Fig. 2. A detailed description of these results is available in Appendix 1.

In adults with ADHD treatment with stimulants (OROS-methylphenidate, IR-methylphenidate, Lis-dexamphetamine, methylphenidate-ER, methylphenidate transdermal system) and atomoxetine had a moderate effect on EL (9 studies, SMD = −0.41; 95% CI: −0.57 to −0.25, $z = 5.14$, $P = 2.7 \times 10^{-7}$) and a large effect on ADHD symptoms (9 studies, SMD = −0.8; 95% CI: −1.07 to −0.53, $z = 5.85$, $P = 4.9 \times 10^{-9}$). There was evidence of high heterogeneity in both analyses ($X^2 = 27.40$, $I^2 = 70.8\%$, $P = 0.001$; $X^2 = 72.09$, $I^2 = 88.9\%$, $P < 0.001$, respectively). There was no evidence of publication bias.

3.4. Subgroup analysis

Main effects from the sub-group analyses are shown in Table 8.

Outcome measure: In the subgroup analysis of studies using the WRAADDS-EDS as a measure of EL, a higher treatment effect was found for EL symptoms (6 studies, SMD = −0.54; 95% CI: −0.75 to −0.33, $z = 5.02$, $P = 5.2 \times 10^{-7}$), compared to the treatment effect of ADHD medication on EL measured by the BRIEF-A (3 studies, SMD = −0.19; 95% CI: −0.33 to −0.05, $z = 2.66$, $P = 0.008$).

Medication class: In the subgroup analysis of stimulants only, a higher effect size was found on EL symptoms (6 studies, SMD = −0.57; 95% CI: −0.80 to −0.34, $z = 4.90$, $P = 9.6 \times 10^{-7}$), compared to the small effect of atomoxetine on EL (3 studies, SMD = −0.21; 95% CI: −0.34 to −0.08, $z = 3.25$, $P = 0.001$).

Table 5
Description of studies included in quantitative and qualitative synthesis.

First Author Disorder Country	Mean age, years (% male) Meds	Supplements (dose/day)		Study duration	Design % completed	Domain(s) investigated	Numbers recruited	
		Active 1	Placebo				Active	Placebo
Reimherr et al. (2007) Clinical ADHD US	30.6 Mixed (66)	OROS- MPH (18/27-90mg)	Unspecified	4 weeks	RCT 87.24%	Emotional lability ADHD Symptoms	20 20	20 20
Wender et al. (2011) ADHD USA	36.9 (72.41) Unmedicated	Immediate release MPH 45 ± 14mg day	Unspecified 49 ± 13 mg/day	2 weeks	RCT 90.5%	Emotional lability ADHD symptoms	58 58	57 57
Reimherr et al. (2005) Clinical ADHD USA/Canada	41.2 (65) Unmedicated	ATX (60mg, 90mg, 120mg)	Unspecified	10 weeks	RCT 84.2%	Emotional lability ADHD symptoms	225 225	226 226
Adler et al. (2013) ADHD symptoms USA	34.2 (active) 34.9 (placebo) (50.6) Unmedicated	Lisdexamphetamine 30mg, 50mg, 70mg (titration)	Unspecified	10 weeks	RCT 78.5%(active) 66.2% (placebo)	Emotional lability ADHD symptoms	79 79	75 80
Adler et al. (2014) Clinical ADHD USA	24.7 (57.30) Unmedicated	ATX 40mg/dayfor min 7 days (20mg BID), 80mg/day for min 7 days (40mg BID). Up to 100mg/day (50mg BID) titration	Unspecified	12 weeks	RCT 79.73%	Emotional lability ADHD symptoms	161 192	167 199
Rosler et al. (2010) ADHD symptoms Germany	35.2 (active) 33.8 (placebo) (50) Unmedicated	MPH-ER 10-60mg/day	10mg capsules	24 weeks	RCT 30.64% (24% active group, 43% placebo group)	Emotional lability ADHD symptoms	241 239	118 118
Merchant et al. (2011) Clinical ADHD USA	18-65 years (unspecified but mixed) Unmedicated	MTS 22% 10-15mg, 28% 20-25mg, 50% 30mg	Unspecified	4 Weeks	RCT 86.5%	Emotional lability ADHD symptoms	26 26	33 33
Goto et al. (2011) ADHD Asia	32.3 (47.70) unmedicated	ATX 40-120mg/once daily	Unspecified	10 weeks	RCT 79.49% ATX 87.25% Placebo	Emotional lability ADHD symptoms	178 191	190 195
Retz et al. (2012) Clinical ADHD Germany	36.6 (MPH), 38.2 (PL) (38- MPH), (56- PL) Unmedicated	MPH-ER 40,60,80,120 md/day	Unspecified	8 weeks	RCT 95.68%	Emotional lability ADHD symptoms	84 83	78 76

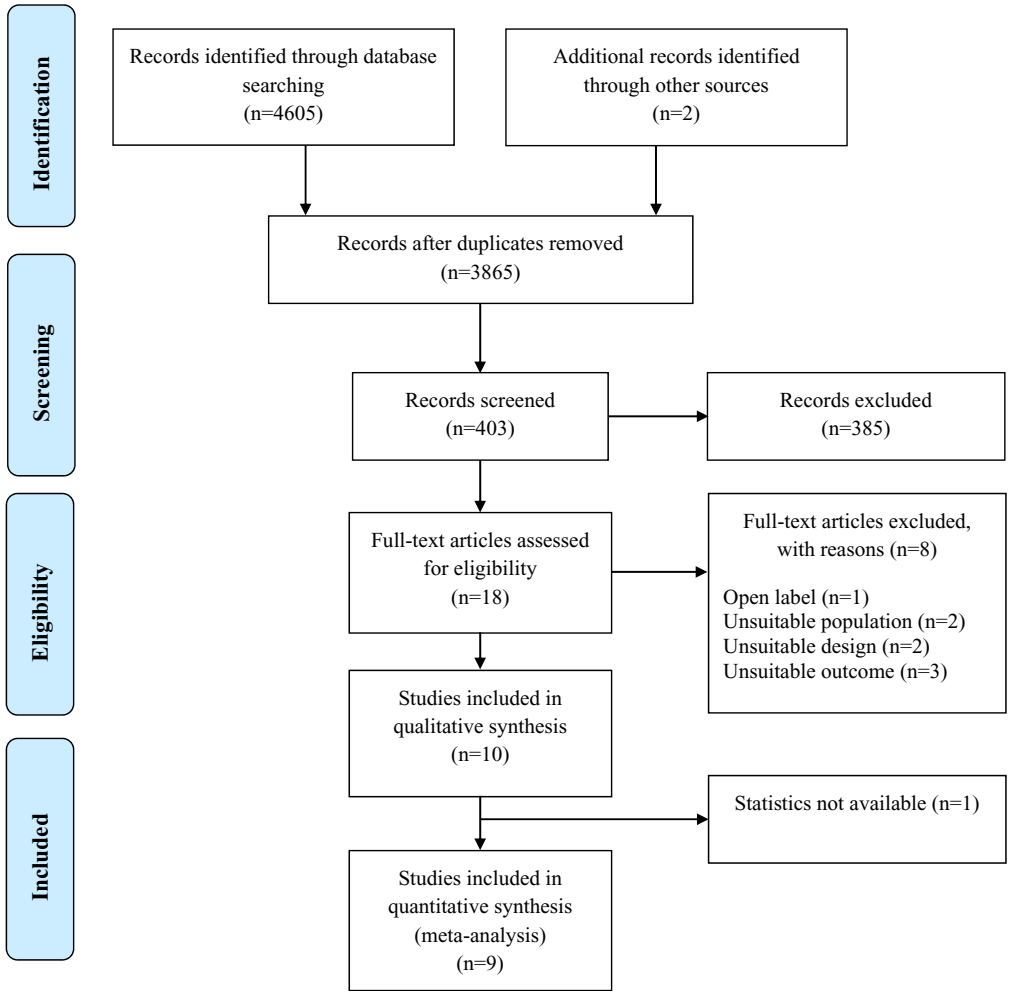

Fig. 1. Prisma flow diagram.

We also looked at the effects of stimulants and atomoxetine on core ADHD symptoms. There was a large treatment effect of stimulants on core ADHD symptoms (6 studies, SMD = −0.98; 95% CI: −1.51 to −0.44, $z = 3.58$, $P = 3.4 \times 10^{-4}$) and a moderate to large treatment effect of atomoxetine (3 studies, SMD = −0.57; 95% CI: −0.68 to −0.45, $z = 9.76$, $P = 1.7 \times 10^{-22}$).

Medication class and outcome measure: There was a large treatment effect of stimulants on EL symptoms when the latter was measured by the WRAADDS-EDS (5 studies, SMD = −0.64; 95% CI: −0.91 to −0.36, $z = 4.46$, $P = 8.2 \times 10^{-6}$).

Atomoxetine had a small effect on EL when this was measured by the BRIEF-A (2 studies, SMD = −0.15; 95% CI: −0.3 to 0, $z = 1.97$, $P = 0.049$).

Table 6
Characteristics of studies included in qualitative synthesis.

Characteristic	Frequencies
N (studies)	9
N (participants)	2,122
% Male[a]	57
Completion rate	77.8%
Medication	Unmedicated: 8 Unspecified: 1 Weighted mean
Age (years)[b]	34.02
Trial duration (weeks)	8.9
MPH (daily dose)	Ranging from 10 mg to 120 mg/day
ATX (daily dose)	Ranging from 40 mg to 120 mg/day

[a] One study did not specify sex ratio's and was therefore not included in this calculation (Marchant et al., 2011).
[b] One study did not specify the mean age but only gave an age range of the participants eligible to take part in the trial, therefore not included in this calculation (Marchant et al., 2011).

Table 7
Studies excluded at full text stage with reasons ($n = 8$).

Reason for exclusion	Studies
Open label	Sobanski et al. (2012)
Unsuitable population	Drijgers et al. (2012) Young et al. (2013)
Unsuitable design	Kavoussi et al. (1993) Du Paul et al. (2012)
Unsuitable outcome	Brown et al. (2011) Wender et al. (1985) Medori et al. (2008)
Statistics not available	Adler et al. (2014)

4. Discussion

We conducted a systematic review and meta-analysis examining the efficacy of stimulants (methylphenidate and dexamphetamine/lisdexamfetamine) and atomoxetine on EL in adults. In addition, we reported on the effects on ADHD symptoms in the same studies to enable a comparison of medication effects on ADHD and EL. Overall we found an effect of stimulants and

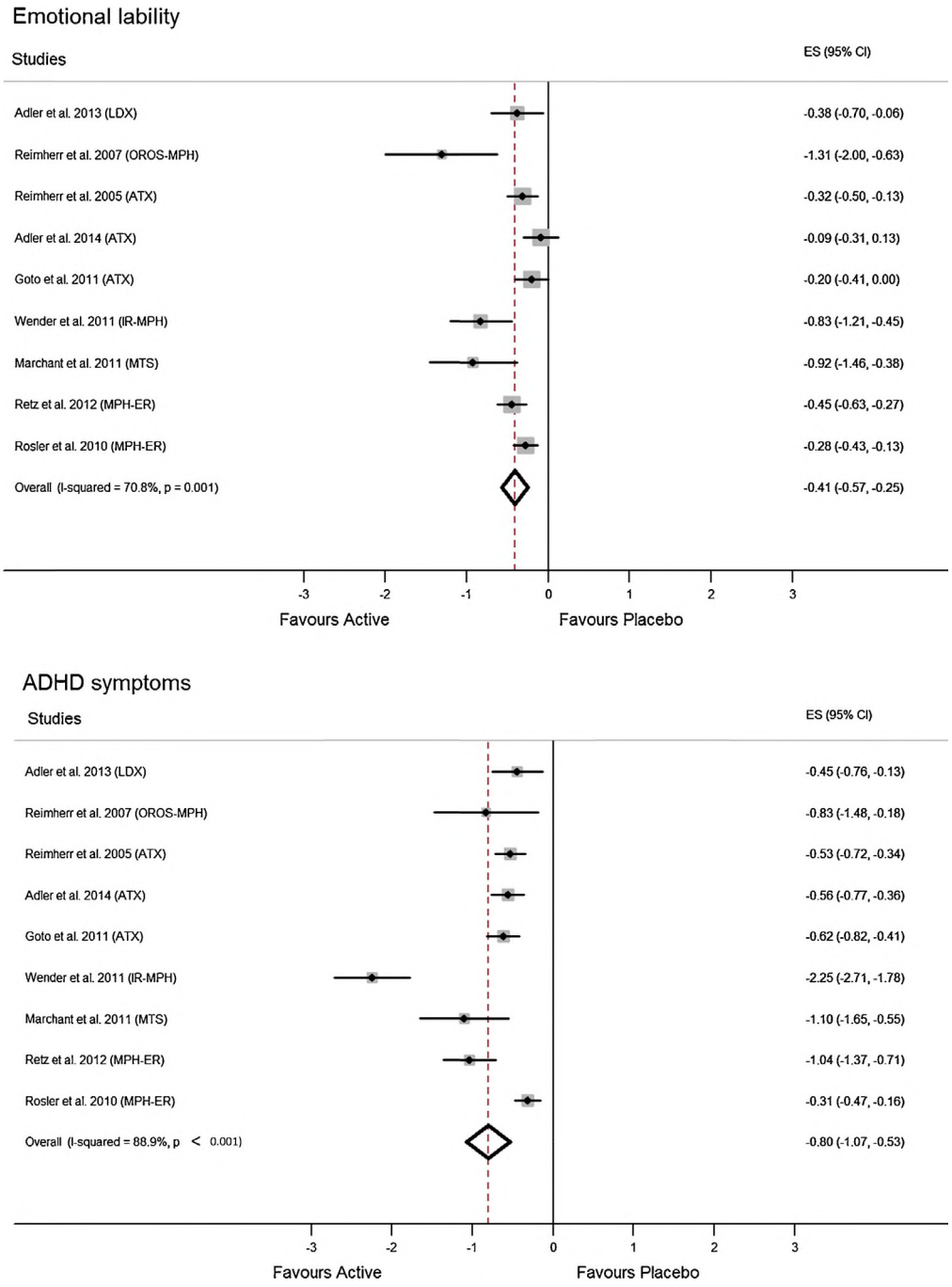

Fig. 2. Forests plots for meta-analyses across the two main outcome domains ES = Effect size.

Table 8
Subgroup meta-analyses of studies based on: (1) Outcome measure (2) medication class and (3) medication class and outcome measure.

	Sub-analyses domain	Studies	*P*	SMD[a]	95% CI
1	WRAADDS-EDS	2,3,6–9	5.2×10^{-7}	−0.54	−0.75 to −0.33
	BRIEF-A-BRI	1,4,5	0.008	−0.19	−0.33 to −0.05
2	Stimulants on EL	1,2,6–9	9.6×10^{-7}	−0.57	−0.80 to −0.34
	Atomoxetine on EL	3–5	0.001	−0.21	−0.34 to −0.08
	Stimulants on ADHD	1,2,6–9	3.4×10^{-4}	−0.98	−1.51 to −0.44
	Atomoxetine on ADHD	3–5	1.7×10^{-22}	−0.57	−0.68 to −0.45
3	WRAADDS-EDS +Stimulants	2,6–9	8.2×10^{-6}	−0.64	−0.91 to −0.36
	BRIEF-A-BRI + Atomoxetine	4,5	0.049	−0.15	−0.3 to 0

Studies: 1 = Adler et al. (2013) [31]; 2 = Reimherr et al. (2007) [30]; 3 = Reimherr et al. (2005) [17]; 4 = Adler et al. (2014) [29]; 5 = Goto et al. (2011) [32]; 6 = Wender et al. (2011) [33]; 7 = Marchant et al. (2011) [19]; 8 = Retz et al. (2012) [18]; 9 = Rösler et al. (2010) [9].

[a] Negative SMD favours a treatment effect for the active medication (stimulants or atomoxetine); Positive SMD favours a treatment effect for the placebo group.

atomoxetine of d = 0.41 (CI: −0.57 to −0.25) for EL symptoms and d = 0.8 (CI: −1.07 to −0.53) for ADHD symptoms. Our findings suggest that medications used to treat ADHD also have a significant effect on EL, although the effect appears to be more modest on EL compared to the effect on the core ADHD symptoms of inattention and hyperactivity-impulsivity.

Subgroup analyses indicated that use of the WRAADDS-EDS as an outcome measure might lead to greater estimates of clinical effectiveness of ADHD medications on EL than use of the BRIEF-A-BRI scale. Subgroup analyses also indicated that stimulants might have a stronger effect on reducing EL symptoms than atomoxetine. The greater effects of stimulants compared to atomoxetine on EL is in line with independent findings from meta-analyses of these medication on core ADHD symptoms [34,35].

Consistent with this, the greatest effect on EL was found when analysing the subgroup of 5 studies which examined the effects of stimulants on EL measured by the WRAADDS-EDS (d = 0.64). These findings suggests that the effect sizes on EL found in this meta-analysis may have been affected by measurement bias or differences in the effects of medication class (i.e. stimulants compared to atomoxetine).

In this meta-analysis stimulants and atomoxetine had a two-fold higher treatment effect on core ADHD than on EL symptoms. Nevertheless, the moderate treatment effect shows clinically significant improvement in the symptoms of EL. One study that was included in the qualitative but not the quantitative analysis also found a significant treatment effect of atomoxetine compared with placebo on EL. Patients receiving atomoxetine had a significant reduction of EL symptoms measured by the BRIEF-A self-rated and informant-rated scales [36].

There were a number of limitations associated with this systematic review. First, despite adopting a broad approach towards the selection of studies, many did not meet the eligibility criteria and we were only able to include half of those assessed for eligibility (9 studies) in the meta-analysis. Secondly, there was substantial heterogeneity with regard to patient groups, assessment measures (including differences in informant versus self-report vs investigator-rated measures) and quality of studies and we therefore had to use random-effects models that produced wide confidence intervals. Thirdly, all the studies included in the meta-analysis relied on participants who were selected on the grounds of having high levels of core ADHD symptoms, not EL symptoms and this may have contributed to the differential effect sizes. No studies of stimulants or atomoxetine on EL symptoms were found for conditions other than ADHD, and none of the trials examined the effects of ADHD medication on EL as a primary outcome. Finally, none of the studies reported standard deviation of the change (the difference before and after the intervention) in their effect size calculations [26] and so we had to rely on the pre-treatment standard deviation in our calculations. This may also have contributed to an underestimation of the true effect size associated with EL [37].

Another limitation was in relation to the different duration of the included trials that may have influenced the result on EL. Therefore a meta-regression of trial duration on both ADHD and EL symptoms has been conducted. However, due to the small number of studies and heterogeneity of study characteristic, the results were inadequate.

In conclusion, our findings indicate that EL in patients with ADHD can be treated with stimulants or atomoxetine. Although these medications reduce EL, the effects appear to be modest by comparison with the effects on the core ADHD symptoms of inattention and hyperactivity-impulsivity. Our findings require replication, particularly in patients selected for high baseline levels of EL and addressing methodological issues such as measurement bias and the potential differential effects of stimulants and atomoxetine.

With regard to the clinical implications of our findings, there are two main possibilities to consider. First, that EL reflects a heterogeneous domain of psychopathology that results from a number of distinct processes requiring different treatments, much in the same way there are different causes for fever or headache. In this scenario it would be important to distinguish between stimulant and atomoxetine responsive and non-responsive forms of EL particularly in ADHD. An alternative explanation is that stimulants and atomoxetine may have a more modest effect on EL overall, perhaps indicating the need for additional targeted psychological treatments in some cases. For example, dialectical behaviour therapy has proven efficacy in the treatment of emotional instability in people with borderline personality disorder [38], and may also have similar effects in ADHD accompanying pharmacological treatments [39]. Further investigations are required using individual patient level data to address these questions.

Finally, we did not find any studies of ADHD drug treatments in adult ADHD patients with comorbid conditions in which emotional symptoms are also prominent. Further studies are therefore required to clarify the role that stimulants or atomoxetine play in the treatment of EL in patients with ADHD and co-occurring conditions such as borderline personality disorder, or bipolar disorder. Notwithstanding, clinicians should be aware that symptoms of EL are often reduced when treating patients with stimluants or atomoxetine who meet diagnostic criteria for ADHD.

Contributors

TRM, PA and PM conceived the study; TRM, REC and EV conducted the literature search and statistical analysis. TRM, REC, PA and PM were involved in the selection of papers. TRM, REC, PA, PM and EV interpreted the data. The manuscript was drafted by TRM and thoroughly revised by PA, PM, EV and REC.

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Disclosure of interest

Philip Asherson, on behalf of King's College London (non-personal pecuniary funds), has served as consultant for Janssen-Cilag, Eli Lilly, Shire, Novartis and has received educational or research grants from or has spoken at sponsored talks from Janssen, GW Pharma, Vifor Pharma, and QbTech. Paul Moran has received funds for sponsored talks for Wiley. Talar Moukhtarian, Ruth Cooper and Evangelos Vassos declare no conflicts of interest.

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Appendix 1. Detailed description of meta-analyses results

Emotional lability

Nine trials in 2,036 adults with ADHD examined emotional lability. There was a moderate effect of stimulants and atomoxetine on EL (SMD = −0.41; 95% CI: −0.57 to −0.25, $z = 5.14$, $P = 2.7 \times 10^{-7}$) with evidence of significant high heterogeneity ($X^2 = 27.40$, $I^2 = 70.8\%$, $P = 0.001$).

ADHD symptoms

Nine trials in 2,097 adults with ADHD examined combined ADHD symptoms. There was a large effect of stimulants and Atomoxetine on core ADHD symptoms (SMD = −0.8; 95% CI: −1.07 to −0.53, z = 5.85, $P = 4.9 \times 10^{-9}$) with evidence of high significant heterogeneity ($X^2 = 72.09$, $I^2 = 88.9\%$, $P < 0.001$).

Emotional lability (WRAADDS-EDS)

Six trials in 1,186 adults with ADHD examined EL using the emotion dysregulation subscale (EDS) of the WRAADDS. There was a medium effect of stimulants and ATX on EL (SMD = −0.54; 95% CI: −0.75 to −0.33, z = 5.02, $P = 5.2 \times 10^{-7}$) with evidence of significant heterogeneity ($X^2 = 18.78$, $I^2 = 73.4\%$, $P = 0.002$).

Emotional lability (BRIEF-A-BRI, emotional control subscale)

Three trials in 850 adults with ADHD examined EL using the emotional control subscale of the BRIEF-A. There was a small significant effect of stimulants and ATX on EL (SMD = −0.19; 95% CI: −0.33 to −0.05, z = 2.66, $P = 0.008$) with no evidence of heterogeneity ($X^2 = 2.17$, $I^2 = 7.9\%$, $P = 0.337$).

Emotional lability (Stimulants)

Six trials in 889 adults with ADHD examined effects of stimulants on EL. There was a medium to large effects of stimulant medication on EL (SMD = −0.57; 95% CI: −0.80 to −0.34, z = 4.90, $P = 9.6 \times 10^{-7}$), with evidence of heterogeneity ($X^2 = 17.76$, $I^2 = 71.8\%$, $P = 0.003$).

Emotional lability (Atomoxetine)

Three trials in 1,147 adults with ADHD examined effects of Atomoxetine on EL. There was small significant effect of ATX on EL (SMD = −0.21; 95% CI: −0.34 to −0.08, z = 3.25, $P = 0.001$) with no evidence of heterogeneity ($X^2 = 2.42$, $I^2 = 17.3\%$, $P = 0.298$).

ADHD symptoms (Stimulants)

Six trials in 889 adults with ADHD examined effects of stimulants on core ADHD symptoms. There was a large treatment effect of stimulants on ADHD symptoms (SMD = −0.98; 95% CI: −1.51 to −0.44, z = 3.58, $P = 3.4 \times 10^{-4}$), with evidence of significant heterogeneity ($X^2 = 71.47$, $I^2 = 93\%$, $P < 0.001$).

ADHD symptoms (Atomoxetine)

Three trials in 1,228 adults with ADHD examined effects of Atomoxetine on core ADHD symptoms. There was a moderate to large treatment effect of ATX on ADHD symptoms (SMD = −0.57; 95% CI: −0.68 to −0.45, z = 9.76, $P = 1.7 \times 10^{-22}$) with no evidence of heterogeneity ($X^2 = 0.4$, $I^2 = 0\%$, $P = 0.817$).

Emotional lability (WRAADDS-EDS + stimulants)

Five trials in735 adults examined the effects of stimulants on EL when measured by the WRAADDS-EDS. There was a large treatment effect of stimulants on EL (SMD = −0.64; 95% CI: −0.91 to −0.36, z = 4.46, $P = 8.2 \times 10^{-6}$) with evidence of significant heterogeneity ($X^2 = 17.66$, $I^2 = 77.4\%$, $P = 0.001$).

Emotional lability (BRIEF-A + Atomoxetine)

Two trials in 696 adults examined the effects of atomoxetine on EL when this was measured by the BRIEF-A-BRI. There was a small treatment effect of ATX on EL (SMD = −0.15; 95% CI: −0.3 to 0, z = 1.97, $P = 0.049$), with no evidence of heterogeneity ($X^2 = 0.56$, $I^2 = 0\%$, $P = 0.45$).

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Chapter 7: Discussion

7.1 Abstract

The overall aim of this thesis was to further our understanding of the association between attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD). This was accomplished by bringing together a diversity of methodologies and approaches to investigate some of the key underlying clinical features that are seen in both disorders. In this chapter, I provide a brief summary and interpretation of the key findings for each chapter separately with respect to the thesis aims. I then discuss common emerging themes from this thesis and present wider clinical implications along with suggestions for future directions, and finally present the main strengths and limitations of the research.

7.2 Overview of key findings

To further understand the associations between ADHD and BPD in women, in **Chapter 3**, latent class analysis (LCA) was undertaken on a sample of female controls, and selected groups meeting DSM-5 diagnostic criteria for ADHD, BPD and comorbid ADHD/BPD. The aim was to validate the classification of the clinical cases using an empirical approach to identify exclusive classes differing in profiles of adult symptoms of ADHD and BPD. First, the latent classes were examined in relation to the DSM-5 classification of ADHD and BPD. Secondly, the latent classes and DSM-5 groups were used to explore the sample's characteristics on various measures of psychopathology. The findings showed that the LCA and DSM-5 diagnostic classification groups cross-validate well, indicating the validity of the constructs used. Regarding the phenotypic characteristics of the sample, overall the empirical and DSM-5 diagnostic approaches gave comparable results. Emotional dysregulation, excessive spontaneous mind wandering, anxiety, childhood maltreatment and impairments in various domains of everyday life, all measured by retrospective questionnaires, reflected non-specific symptoms, risk factors and outcomes that were seen across both disorders and could not be relied upon to discriminate ADHD from BPD. Furthermore, the ADHD and BPD groups were not completely distinct. Both DSM-5 and LCA classification approaches showed that one disorder does not appear without the presence of some of the core symptoms of the other disorder. Yet, despite the overlap of certain symptoms in ADHD and BPD,

the cluster of several of the core symptoms in each disorder (which were measured by the diagnostic interviews of the disorders), and the threshold counts (reflecting clinical syndromes rather than symptoms), appear to be specific enough to systematically delineate the disorders from one another.

One methodological limitation of the first study (chapter 3) was the reliance on retrospective rating scale data, which could be prone to a variety of recall biases. The second (chapter 4) and third (chapter 5) studies summarised below, circumvented these problems by using prospective (real time experience sampling) data collection methods.

Chapter 4 and chapter 5 aimed at investigating excessive spontaneous mind wandering, and emotional dysregulation respectively, as two components of psychopathology that might distinguish ADHD from BPD. In these studies, an experience sampling method (ESM) was used, in which participants rated symptoms of mind wandering and emotions eight times daily over a period of five days.

Chapter 4 reports that similar levels of mind wandering in both ADHD and BPD diagnoses are found, suggesting that excessive mind wandering leading to inattentiveness may be a greater problem in the daily lives of individuals with BPD than generally recognised. Nonetheless, the type of mind wandering in ADHD appeared to be distinctive. In ADHD mind wandering seemed to reflect a core characteristic of the disorder that was not accounted for by symptoms of anxiety or depression, whereas in BPD mind wandering was accounted for by levels of anxiety and depressive symptoms.

In **chapter 5**, using a similar ESM approach, intensity and instability of positive and negative emotions, as well as the influence of daily adverse events on these emotions were investigated. ADHD and BPD showed similar levels of emotional instability for positive and negative symptoms, and some differences in the intensity of *happy*, *sad*, and *angry*. Significant differences between the groups were accounted by the level of anxiety and depression symptoms. Additionally, neither the increased intensity nor instability of emotions in the clinical diagnoses could be fully accounted by increased frequency and impact of bad events, reflecting a reactive and an endogenous nature of emotional dysregulation in both ADHD and BPD.

Chapter 6 provided the most conclusive evidence to date that treatment with stimulants and atomoxetine has a clinically significant effect on reducing symptoms of emotional dysregulation in adults with ADHD. Stimulants (methylphenidate and dexamphetamine/lisdexamphetamine) and atomoxetine were moderately effective for reducing symptoms of emotional dysregulation, while effect sizes on core ADHD symptoms (inattentive and hyperactivity/impulsivity) were twice as large. However, cases in these studies were selected for high levels of ADHD symptoms and not emotional dysregulation. Furthermore, there was some evidence that effects were greater with stimulants than atomoxetine, requiring further investigation. A more recent systematic review and meta-analysis, also assessing the effects of ADHD medication on symptoms of emotional dysregulation in adults, showed small-to-medium effects (Lenzi, Cortese, Harris, & Masi, 2017), slightly lower than the meta-analysis I conducted. Several methodological differences could explain this discrepancy. First, Lenzi et al. (2017) included six additional trials with a cross-over design, which was an exclusion criterion in my study, and another two trials in which the active medication under investigation was duloxetine and bupropion. These two have a different mode of action from stimulants or atomoxetine, are not validated as effective treatments for ADHD according to the NICE guidelines (NICE, 2018), and therefore were excluded from my study. Second, three trials were published after the search and selection phase of the current study ended.

Overall, emotional dysregulation was found to be less responsive to stimulants and atomoxetine than core ADHD symptoms, perhaps indicating the need for adjunctive psychotherapy in medication non-responsive forms of emotional dysregulation in adults with ADHD.

7.3 General discussion

Overall, this thesis addresses several gaps in the literature and clinical understanding of the nature of the relationship between ADHD and BPD.

All the data chapters in this thesis point to the transdiagnostic nature of the overlapping symptoms of ADHD and BPD and of related impairments in various life domains, reflecting the heterogeneous picture of both conditions. Results from the

LCA and DSM-5 classifications of the disorders showed that symptoms of BPD were not found to occur without at least some ADHD symptomatology and vice versa.

7.3.1 Towards a dimensional classification

The empirical findings of this thesis challenge the value of the categorical classification of ADHD and BPD, supporting instead a more dimensional and symptom-led approach of classification. For example, heightened intensity and instability of emotional symptoms, and frequency of mind wandering, were seen in both ADHD and BPD. Furthermore, subthreshold ADHD was seen in BPD cases and vice versa, indicating the somewhat arbitrary nature of the designated symptom count thresholds for both disorders. Chapter 3 showed that the BPD only class, in addition to the BPD symptoms, also showed high probability for "difficulty sustaining attention", which mostly characterises symptoms of mind wandering. This was then directly supported by the findings in chapter 4, where the BPD diagnosis showed equally heightened and more frequent mind wandering as the ADHD diagnosis.

Regarding the LCA analyses, one could argue that the findings reported in chapter 3 did not provide any novel finding, but rather showed a circular pattern of investigation because of the selected nature of the sample based on DSM-5 criteria. However, the LCA analysis was taken in addition to the DSM-5 classification because I was concerned about the use of pre-defined symptom thresholds and wanted to check that a more empirical approach to classifying the diagnostic groups (not relying on pre-determined symptom count thresholds) would not lead to significant changes in the results of the study. For example, LCA might have provided better separation of the groups than using the pre-defined DSM-5 criteria. This concern became apparent during data collection, when by using the thresholds set out to separate one condition from the other, some individuals fell just above or below the designated symptoms thresholds. I wanted to check whether a more symptom-based empirical approach would re-classify individuals who laid on one side or the other of these thresholds set out in the DSM-5. With only few cross-over cases and despite the overlap of individual items, the LCA showed comparable classification and results, as the DSM-5 criteria. Nonetheless, there was a large

number of variables used in the LCA and a rather small sample size for this type of analysis, which statistically prevented the selection of a solution with more than four classes. Future studies using LCA to separate ADHD from BPD, should aim at replicating these findings in larger epidemiological samples unselected for high ADHD and BPD symptoms.

The findings from this thesis suggest that the overlap of ADHD and BPD does not reflect how the disorders are classified, where there appears to be good distinction, but rather concerns the overlap of individual symptoms. This is one reason why emotional dysregulation is only specified as an 'associated feature' of ADHD supporting the diagnosis in DSM-5 (American Psychiatric Association, 2013) rather than a core symptom used in the classification of ADHD, as it is also seen in BPD and other disorders. Emotional dysregulation appears to reflect a heterogenous domain of psychopathology present as a transdiagnostic symptom in ADHD and BPD, as well as in other psychiatric disorders such as post traumatic disorder and bulimia nervosa (Santangelo et al., 2014). So, it is intuitive to question the specificity of emotional dysregulation in BPD as a core diagnostic criterion, when it has been shown both in the literature and in the current thesis that it cannot be used to delineate it from other disorders. In fact, both ADHD and BPD reflect impairing extremes of dimensional traits (Chen et al., 2008; Clark, 2007), thus it is also intuitive to see symptoms of these disorders across a wide range of psychiatric conditions, as well as in healthy populations. Future studies could extend on the findings of emotional dysregulation and mind wandering reported in this thesis and utilise ESM in ADHD and BPD to investigate other core BPD symptoms such as identity disturbance, chronic feelings of emptiness or suicidality, where differences between the disorders might emerge.

This potentially contributes to a lack of awareness of ADHD as a differential diagnosis for clinicians encountering adult patients with emotional dysregulation. Asherson (2005) and Wender, Wolf, and Wasserstein (2001) noted that adults with unrecognised ADHD are not infrequently misdiagnosed and treated for anxiety, depression, mixed affective disorder, cyclothymia, and borderline and unstable personality disorders. In the debate on the differentiation between ADHD and BPD, it has been suggested that since mood symptoms are not core symptoms of ADHD,

their presence as a major presenting problem suggests the presence of a mood disorder rather than ADHD (Wilens, et al., 2003). This interpretation could be in line with my finding whereby anxiety and depression symptoms accounted for emotional dysregulation in both ADHD and BPD. However, findings from converging evidence (genetics, treatment effects, impact on ADHD-associated impairment) does not support this assertion (Asherson, Buitelaar, Faraone, & Rohde, 2016). For example, Skirrow et al. (2014) found high levels of emotional dysregulation that had an independent effect on ADHD-associated impairment, in adult males with ADHD, where comorbid anxiety and depression disorders had been carefully excluded.

The results presented here further extend the findings of Skirrow et al. (2014) by showing that emotional dysregulation in women with ADHD is elevated and is comparable to the pattern of emotional dysregulation seen in BPD. This fills an important gap in the literature, since to date it has not been possible to clarify whether emotional dysregulation has a similar profile in ADHD as it does in BPD.

These findings suggest that ADHD should be considered an important differential diagnosis when encountering patients with unstable emotional symptoms; particularly in light of the meta-analytic (chapter 6) work presented in this thesis showing a good clinical response of emotional dysregulation to stimulants and atomoxetine when treating adults with ADHD. Overall, given the symptom overlap, clinicians should always consider the presence of ADHD or BPD when diagnosing the other condition and there should be more awareness of the co-occurrence of these disorders in mental health services.

Findings in chapter 4 further support the phenotypic overlap between ADHD and BPD since, despite my prior hypothesis, high frequency of mind wandering was not specific to ADHD. However, depression and anxiety symptoms accounted for mind wandering in BPD, but not ADHD, pointing to the idea that MW in BPD most likely reflects depressive and anxious rumination, which is not uncommon in BPD populations (Stepp, Scott, Jones, Whalen, & Hipwell, 2016). In ADHD it is thought that the content of MW is less constrained, with no pattern of repeated thoughts or abnormality of content (Asherson et al., 2016; Christoff, Irving, Fox, Spreng, & Andrews-Hanna, 2016). This is supported to some extent by the ESM finding in

chapter 4 of more negative content of mind wandering in BPD compared to controls, whereas the pattern of negative thoughts seen in ADHD was similar to than seen in controls. Yet, these findings need to be replicated in future studies specifically assessing the content of mind wandering (and not just the nature of content as defined in this study by 'pleasant' versus 'unpleasant' thoughts), and how this might differ across disorders.

The issue of delineating overlapping psychiatric disorders has been shown in neurophysiological and neurobiological research. For example, as evidenced by the difficulties encountered in identifying polygenic risk scores that are specific to phenotypes, with considerable evidence for shared genetic aetiology across mental health disorders from large scale genome-wide association studies (GWAS) (Demontis et al., 2017). Similarly, overlap between functional neuroimaging findings is commonly seen when comparing between mental health disorders (Broyd et al., 2009).

Such matters have led to proposals by the National Institute of Mental Health of the Research Domain Criteria (RDoC), which suggests that researchers now need to move beyond categorical definitions of psychiatric disorders, to directly study common underlying impairments in neurocognitive systems that cross traditional diagnostic boundaries (Insel et al., 2010). The RDoC proposes that dimensional cross-disorder measures of symptoms and their neurobiological correlates might make better targets for treatment (Insel et al., 2010).

This approach aims to find new ways of grouping or separating clusters of symptoms based on dimensional deviations from typical functioning and conceptualises existing diagnostic categories as the combined profile of several specific cognitive or emotional impairments. It has been suggested that this empirical data-driven neurobiological framework is necessary to tackle the heterogeneity and comorbidity observed in current clinical diagnostic categories such as ADHD and BPD, which are thought to be limiting the ability of neurophysiological and genetic studies to identify robust biomarkers, and specific treatments, associated with current disorder concepts (Insel et al., 2010). As one example, within this framework it may be

possible to identify stimulant responsive and non-responsive forms of emotional dysregulation and mind wandering, in both ADHD and BPD.

Future studies might therefore include samples of individuals with common symptoms such as sustained attention deficits and mind wandering, as well as emotional dysregulation and impulsive responding, without having stringently defined diagnostic inclusion categories; and in doing so may then clarify the aetiologies of specific deficits at a level below that of clinical diagnosis, that would ultimately map better to specific treatments. This approach may also improve conceptualisation of co-occurring symptoms and disorders, which may or may not have common shared genes, environmental factors, and shared neurobiology. Such approaches could also include a greater range of participants such as: those with less severe forms of disorders; subthreshold cases not meeting the predefined categorical diagnosis but still impaired and requiring treatment; and those with comorbidities, which are often excluded from current research despite evidence that these are extremely common in psychiatric populations. Such samples would also be more representative of populations likely to present to mental health services, and therefore findings could offer further advantages of being more generalisable to typical clinical populations.

7.3.2 Targeted treatments

The meta-analytic evidence in chapter 6 confirms the clinically significant effect of stimulants and atomoxetine on reducing symptoms of emotional dysregulation in ADHD, yet not as effective as they were on core symptoms of inattention and hyperactivity/impulsivity. This could still however be due to limitations of sample selection for high ADHD symptoms and not symptoms of emotional dysregulation, and investigation of treatment effect on emotional dysregulation as a secondary outcome, as discussed in detail in chapter 6. In chapters 3 and 5, findings show that heightened intensity and instability of emotional dysregulation in ADHD was analogous to that seen in BPD. Therefore, medications such as stimulants could also be effective in reducing symptoms of emotional dysregulation in individuals with co-occurring ADHD and BPD, and in other conditions marked with intense and heightened patterns of emotional dysregulation. Conversely, psychotherapeutic

interventions targeting emotional dysregulation such as dialectical behavioural therapy commonly used in BPD may be helpful for ADHD cases with high levels of emotional dysregulation with partial or no response to ADHD drug treatments. A more nuanced approach to the management of people presenting with both ADHD and BPD is therefore recommended (Moukhtarian, Mintah, Moran, & Asherson, 2018).

Findings in chapter 6 require replication, particularly in patients selected for high baseline levels of emotional dysregulation. However, there are as yet no investigations of ADHD drug treatments in patients with ADHD and comorbid BPD, or ADHD and other comorbidities in which emotional dysregulation is prominent. Further investigations are therefore required to clarify the role of stimulants and atomoxetine on emotional dysregulation in patients with ADHD and co-occurring disorders such as BPD, or bipolar disorder. Further studies are also needed to investigate the causes of lower clinical response, which could be due to the differences between medication respondent and non-respondent types of emotional dysregulation. Discovering markers of clinical response, such as neural biomarkers for example, are essential in developing more effective treatment protocols.

An analogy of emotional dysregulation might be fever in physical health. Fever arises in the context of many different disorders, but the causes and therefore the treatments may or may not be entirely distinct; although some treatments such as anti-inflammatory drugs may have a general effect on reducing fever. Further research is therefore needed to better understand the underlying causes and neurobiological mechanisms of emotional dysregulation across psychiatric disorders and the use and targeting of different treatments.

Finally, there is no data on the response of either ADHD symptoms, excessive mind wandering, or emotional dysregulation in patients with comorbid ADHD/BPD; an important topic for future research.

7.3.3 The effect of depression and anxiety symptoms

The general role of depression and anxiety in the findings reported in this thesis on emotional dysregulation, but not mind wandering, is important to consider. Despite

some of the limitations highlighted in the literature about the validity of the BSI subscales of depression and anxiety as diagnostic tools (Petkus et al., 2009), the aim here was to use it as a measure of anxiety and depressive symptom severity. ADHD and BPD showed comparable levels of anxiety and depression on the scales. Regarding emotional dysregulation, depression and anxiety had a similar relationship in ADHD and BPD as discussed in chapter 5, accounting for the differences found between the two disorders, and between the disorders and controls. In contrast, as discussed in chapter 4, in ADHD mind wandering seems to be independent of anxiety and depression, potentially reflecting a core characteristic of the disorder (Bozhilova, Michelini, Kuntsi, & Asherson, 2018); but in BPD potentially reflecting an underlying mechanism driving mind wandering. This was further supported by the significant findings on the unpleasant (i.e. negative) content of mind wandering in the BPD diagnoses, which were also driven by depression and anxiety. Although the results were somehow inconclusive, mind wandering about something unpleasant may reflect anxious thoughts and depressive ruminations in BPD, commonly reported in this population (Peters et al., 2017). Further studies should be conducted specifically examining the role of anxious and depressive symptoms in ADHD and BPD, their underlying neurobiological mechanisms and their relationship to overlapping symptoms such as emotional dysregulation and mind wandering, before further conclusions can be made.

7.4 Strengths and general limitations

7.4.1 Sample characteristics

7.4.1.1 Exclusion criteria

From the participant sampling procedure described in Chapter 2, it can be seen that due to stringent exclusion criteria, many individuals referred to the ADHD and BPD specialist clinics were not eligible to participate in the Personality Research in Emotional Instability and ADHD (PRIDE) study. This gave rise to two major limitations for this study. The first is that results may not generalise to many adults with ADHD, BPD or comorbid ADHD/BPD, who are frequently affected by comorbid psychiatric conditions and/or are on psychoactive medication (particularly mood stabilisers and anti-psychotics). The second is the resulting small sample size,

which may have been underpowered for some investigations, where trending results were identified, and tests frequently did not withstand correction for multiple testing.

Current guidance from the National Institute for Health and Care Excellence (NICE, 2009) states that drug treatments should "not be used for borderline personality disorder or for the individual symptoms or behaviour (e.g. repeated self-harm, marked emotional instability, risk-taking behaviour and transient psychotic symptoms) associated with the disorder". Nevertheless, many BPD patients without comorbidities requiring treatment, were on psychoactive medications, and did not meet the inclusion criteria for this study. This led to considerable challenges for recruitment of the BPD sample. This was not surprising and in line with the findings from Crawford et al. (2011), who showed that individuals with an emotionally unstable personality disorder were more often prescribed with psychotropic medication (anti-depressants, anti-psychotics, benzodiazepine, mood stabilisers and hypnotic drugs) than those being treated for other personality disorders. They also found that individuals being treated for a personality disorder, despite the available guidance and lack of evidence, were prescribed at least one psychotropic medication, and one in five was prescribed three or more (Crawford et al., 2011).

The restricted sampling procedure can also be considered a strength to the study. There is a disadvantage of including individuals with comorbid conditions or on psychoactive medications regulating symptoms commonly associated with ADHD and BPD, in a study with the primary purpose of investigating the overlap of symptoms between the disorders. This is because it then becomes unclear whether the symptoms which are expressed similarly in these conditions could be due to comorbid conditions or medications. Excluding co-occurring disorders helped to clarify that the overlap detected between ADHD and BPD can be attributed to the overlapping picture of the disorders rather than potential confounders. Additionally, in this cross-disorder comparative analysis of ADHD and BPD, the exploratory nature of the study served as a basis of much larger-scale investigations in the future, by which smaller clinically meaningful differences could be detected.

7.4.1.2 Sex

The sample was limited to female participants, and all results and conclusions in chapters 3, 4, and 5 can therefore only be generalised to females with ADHD and BPD. The initial aim was to include males as well as females in the study sample. However, the low rates of male referrals with BPD and low rates of female referrals with ADHD meant that recruitment of a sex-matched sample within the restricted timeframe of my PhD completion was not feasible. Additionally, given that it is mostly females who receive therapy for BPD while the sex ratio for adult patients with ADHD is more equally divided, the results of this study are more representative for the clinical population with BPD than those with ADHD.

Although this limits interpretation to females, it has the advantage of removing potential sex differences which could confound some of the findings. Additionally, females are generally underrepresented in studies of ADHD, and the study here is complementary to the study of men with ADHD by Skirrow et al. (2014).

Studies aiming to investigate similar research questions in a more sex balanced design would require a much longer duration of study recruitment, and/or less restrictive exclusionary criteria.

7.4.1.3 Clinical heterogeneity

Conceptually, the adoption of stringent inclusion criteria is undertaken to reduce sample heterogeneity by including only those participants meeting certain diagnostic criteria. However, even within these diagnoses, substantial heterogeneity may still be present due to different expressions of symptoms within the disorder between individuals, different aetiologies or other factors such as undiagnosed comorbidities, or the subclinical expressions of population traits which interact with the symptoms of the primary diagnosis.

7.4.2 Diagnostic issues

Diagnostic criteria for ADHD and BPD in the PRIDE study was applied as specified in the DSM-5 (American Psychiatric Association, 2013) (see section 2.3.3.1 in Chapter 2 for details on clinical diagnosis).

According to the DSM-5, ADHD diagnosis requires the presence of several inattentive or hyperactive/impulsive symptoms prior to age 12 years. In the PRIDE study, as mentioned in chapter 2, *several* was defined as three or more, which is the same approach taken by most researchers investigating the age of onset of ADHD and application of the DSM-5 criteria (Agnew-Blais et al., 2016; Polanczyk et al., 2010). Reporting of three or more symptoms in childhood, could however be inaccurate due to problems of retrospective recall, leading to both false positive and negative cases. Furthermore, this relates to recent debate about the existence of late or adult onset forms of ADHD, based on several prospective longitudinal outcome studies of population or control samples. The Dunedin study that kicked off this debate, found that 90% of the individuals with adult ADHD at age 38 did not meet full diagnostic criteria for the disorder in childhood assessed at age 11, 13 and 15 years (Moffitt et al., 2015).

Subsequent studies provided information on late-onset ADHD up to the age of 18 years, but there is as yet no further data up to the age of 38 to confirm or refute the findings reported in the Dunedin study. In another population-based longitudinal study, among those who met criteria for ADHD at age 18 (n=166), 67.5% (n=112) did not meet full ADHD criteria at any of the four childhood assessments (Agnew-Blais et al., 2016). In the large Pelotas Birth Cohort Study (n=5249), at age 11 years childhood ADHD was estimated to be present in 8.9% (n=393) of the sample, while at age 18 to 19 years 12.2% (n=492) fulfilled all DSM-5 criteria for adult ADHD except for age of onset (Caye, Rocha, Anselmi, & et al., 2016). Their findings suggested that 17.2% (n=60) of the children with ADHD continued to meet diagnostic criteria as young adults, while only 12.6% (n=60) of those meeting ADHD criteria as adults would have met the diagnostic criteria for ADHD as children (Caye et al., 2016). These and other more recent studies point to the emergence of the full diagnosis of ADHD during late adolescence (late-onset ADHD) in some cases, although many would meet the DSM-5 criteria of several symptoms by the age of 12 years. However, a full understanding of the emergence of ADHD beyond the childhood years remains to be fully elucidated, and debate remains about the existence of late-onset ADHD and whether it is a distinct disorder with different aetiologies. Investigation of this issue was not within the scope of this thesis, however I discuss this here as it impacted on the classification of few cases (n=5) in my study,

who reported current symptoms and impairments, but not sufficient childhood symptoms, to meet DSM-5 criteria for ADHD.

There are additional concerns regarding the assessment of ADHD in adulthood, particularly when a childhood ADHD diagnosis was not previously established, and onset of symptoms and impairments before age 12 years were determined by retrospective self-reports. A study investigating retrospective diagnoses of ADHD by semi-structured clinical interviews (without informants), showed a high rate of positive diagnosis in a large sample of adults with ADHD who had previously been diagnosed with ADHD as children (78%), however the rate of false positive classifications in control participants was also relatively high (11% (Mannuzza, Klein, Klein, Bessler, & Shrout, 2002). This indicates that while some individuals may not be able to recall their childhood symptoms, false positive rates might also be a problem.

Based on these considerations, it was an evident decision to exclude childhood symptoms from the LCA in chapter 3. However, this prevented the investigation of the developmental trajectory of ADHD symptoms from childhood predicting BPD diagnosis, using latent transition analysis. Future studies, particularly investigating symptoms in childhood and adulthood would be best conducted using prospective data from childhood to adulthood but note that this would have to include normative cases since late-onset of ADHD would include children who did not meet full criteria as children. An alternative could be the inclusion of informants, wherever possible, such as parents or siblings who may have known the patients during their childhood, however this does not remove the effects of retrospective report bias for informants.

7.4.3 Treatment issues

Referrals from the ADHD and BPD specialist clinics were done at different time-points in the diagnostic and treatment process, from the moment a patient was admitted to the service to after they have been discharged. This was an issue for some of the participants with BPD referred to the study whilst receiving or after finishing psychological therapies, who could have reported reduced functional impairment and symptom severity, compared to individuals referred at assessment or on a waiting list for treatment. BPD is not as enduring as it was first hypothesised, and

psychological treatments are an evidence based treatment leading to reduced symptom severity and related impairments (Gunderson et al., 2011). The McLean 10-year follow-up study found that BPD improves over time with remission rates (i.e. no longer meeting diagnostic criteria) of around 80% lasting eight years (Zanarini, Frankenburg, Reich, & Fitzmaurice, 2012). The sample was therefore heterogenous regarding symptom severity and non-significant differences across ADHD and BPD could have been due to less severe symptom profiles in BPD than that seen in untreated individuals. Future studies should therefore investigate overlapping features in ADHD and BPD in untreated samples.

Many individuals in the clinical groups, notably in the BPD group, were on concomitant anti-depressants (n=32), which may have reduced the severity of ADHD or BPD symptoms and associated cognitive and functional deficits. In the ADHD sample, there were no differences in the current ADHD ($F(1,30) = 1.7$, $p=.202$) and BPD ($F(1,30) = .01$, $p=.920$) symptoms between those who were on anti-depressants (n=8) and those who were not (n=24). Similarly, in the BPD sample, there were no differences in the current ADHD ($F(1,17) = 1.6$, $p=.223$) and BPD ($F(1,17) = 1.64$, $p=.217$) symptoms between those who were on anti-depressants (n=15) and those who were not (n=4). Finally, in the comorbid ADHD/BPD sample, those who were on concomitant medication (n=9) and those were not (n=18) reported similar ADHD ($F(1,25) = 3.19$, $p=.086$) and BPD ($F(1,25) = .57$, $p=.457$) symptoms. Despite symptoms of ADHD and BPD not being significantly different between those taking anti-depressants and those who were not, it *is* feasible *that* concomitant medications may have led to differences in symptom severity.

7.4.4 Losses to non-attendance

Some problems with recruitment may be considered issues inherent to problems with disorganisation, which is a common feature seen in both ADHD and BPD conditions. Despite a reminder system being in place where all participants received a text message on the day before their appointment with details of their research session, a number of participants did not show up to their scheduled appointments. Five individuals never showed up to their scheduled research assessments, despite

being given multiple appointments. Nonetheless, this was relatively a small proportion (4.4%) in view of the disorganised nature of the conditions.

7.4.5 Measures in the study

An additional limitation was the retrospective and self-report nature of some of the measures used in chapters 3, 4 and 5, which inevitably are prone to bias. The diagnostic interviews may be less prone to this bias since the investigator is asking about specific examples of symptoms and behaviours, however this is still reliant on the accuracy of self-report. Regarding diagnostic interviews, the inclusion of informant reports may increase the accuracy of the assessments, strengthen the findings, and would be an important area in which to extend future investigations. In ADHD, differences between self and informant reports in adults and children (Barkley, Fischer, Smallish, & Fletcher, 2002; Wan Salwina, Baharudin, Nik Ruzyanei, Midin, & Rahman, 2013) have been documented, yet, much less is known about the validity of self-report measures in BPD. Some evidence indicates that patients with BPD overestimate emotions with negative valence and underestimate emotions with positive valence, when comparing retrospective with ESM rating (Ebner-Priemer et al., 2006). However, despite this methodological drawback in diagnostic interviews used to establish presence or absence of symptom criteria, the accuracy of reporting dynamic changes and qualitative characterisation of symptoms of emotional dysregulation and mind wandering, which are internal rather than external symptoms, will have benefitted from the use of prospective ESM measures. By employing this type of ambulatory monitoring in the current study, I was able to reduce the effects of recall-bias.

7.4.6 Multiple testing

Due to the large number of measures employed in this study and therefore the multiple group comparisons conducted, Bonferroni correction was applied where appropriate to account for multiple testing. This rather conservative approach has its limitations. "A *p* value is no substitute for a brain", a quote from Stone and Pocock (2010) emphasising the importance of making interpretations beyond just the significant/non-significant *p* values. When adopting such a strict method to correct for multiple testing, solely based on the number of tests, most often some meaningful

findings disappear (Pocock, McMurray, & Collier, 2015). It is therefore important to make a distinction between statistical significance and clinical relevance of findings, more crucially in studies like the current one, in which a lot of clinical implications can be derived that could benefit patients and clinicians. Nevertheless, findings that arise from studies that are not fully powered for specific a priori hypotheses, should always be considered exploratory, requiring replication(s) to confirm or refute initial observations.

7.4.7 Strengths of the meta-analytic and statistical methods employed

The meta-analysis conducted in chapter 4 offered the most conclusive evidence of the treatment effect of stimulants and atomoxetine on emotional dysregulation in ADHD to date. The analyses were performed to recommended standards for systematic reviews and meta-analysis and care was taken to combine homogenous measures by, for example, having a very conservative approach in including parallel group trials or initial data before cross-over only, and conducting separate analyses for the different outcome measures and medications (stimulants versus atomoxetine) employed in the trials included.

In chapters 4 and 5, multilevel models were used to analyse the longitudinal data collected by ESM. Multilevel models have become the primary method for analysis of clustered data since all available data is used for each subject, and models can effectively handle: 1) data which is correlated within subjects, 2) time effects which differ between participants, 3) binary and continuous covariates which can change over time, and 4) missing data which occurs at random in the dataset (Gueorguieva & Krystal, 2004).

7.5 Concluding remarks

The high level of phenotypic symptom and impairment overlap observed in ADHD and BPD, is a source of confusion for many healthcare professionals. This is particularly true for those who are less familiar with current best practice in relation to the key identifiers and treatment for each disorder. The identification of more objective biomarkers for either disorder may be diagnostically valuable in the future. More generally, as discussed in chapter 1, the shared or specific neurobiological

aetiology of these disorders is still poorly understood, and studies such as those conducted for chapters 4, *5, and 6* represent additional contributions to the growing body of work which ultimately aims to map out a new biologically grounded framework for understanding mental illness. Genetic and/or neurocognitive markers may be considered an important avenue for aiding in establishing differential diagnosis in the future. More cross-disorder studies are required to identify neural and cognitive markers which may be disorder specific or predict response to treatments. It is envisaged that future work will uncover new approaches to classification based on symptoms, biomarkers, rather than disorders, with improved targeting of effective treatments.

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Appendix 1: Telephone screening- Control subjects

Participant Checklist: Exclusion/Inclusion criteria to be checked over the telephone

****CONFIDENTIAL****

Question	**Guidance**	**Answer (Y/N) and notes**
1. Have you EVER had any problems that have troubled you with regards to your mental health?	Exclude if they have had any mental health problems	
2. Have you ever had distinct episodes of depression or sadness different from what you're normally like lasting a week or more? If so, when was this? If no – go to **Q 5**	Exclude if currently experiencing a distinct episode of major depression.	
3. Have you had a period **recently** where you felt sad, depressed, empty or tearful **nearly every day for at least 2 weeks**? If yes: • Did you lose all interest in things, or got no pleasure from things which would usually make you happy? • When did you first feel like this? • Are you still feeling like this?	If answer is yes, try to gauge severity of depressed episode using additional questions. Exclude if currently experiencing a distinct episode of depression	
4. Have you had more than one spell like this in the last 2 years? I mean more than just one period when you have been seriously depressed or anxious	Consider excluding if depression is recurrent	
5. Have you had periods of feeling far more happy or energetic than your usual self, lasting for a week or more? So that your friends told you were talking too fast or that you were too 'hyper, compared to usual? If so, when was this?	Exclude if participant has experienced distinct episodes of mania/elation but not rapid cycling	
6. How often do you have a drink containing alcohol? (Never, Monthly or less, 2-4 times per month, 2-3 times per week, 4+ times per week)		
7. Approximately how many units of alcohol do you drink per day? Recommended limit for women 2-3 Units, for men 3-4 Units. **To calculate:** • Single shot is 1 unit • Alcopop is 2 Units • Can/pint of light beer is 1 unit. • Can/pint of lager is 2 Units • Can/pint of extra strong lager is 4 units • Party cocktail is 5 units • Glass of wine (175ml) is 2 units	Exclude women who drink more than 14 Units a week, roughly spread over 3-4 days.	

8. Do you take any other drugs, legal or illegal? Which ones do you take? And how often do you take these? (prescribed or over the counter medications, cannabis (marijuana, hash), solvents, tranquilizers (Valium), barbiturates, cocaine, stimulants (speed), hallucinogens (LSD) or narcotics (heroin)	Exclude if illegal drugs taken more often than twice weekly.	
9. Have you ever been addicted or dependent on any drugs or alcohol? If so, when was this?	Exclude if major history of drug or alcohol addiction, exclude if current substance abuse or addiction	
10. Have you ever suffered any injury to your head? If yes have you recovered from this/has it affected you in the long-term? Have you suffered from any neurological disorder (e.g. epilepsy, stroke, and dementia)?	Exclude if they feel this has affected them in the long-term (e.g. if symptoms began from the injury). Exclude if answer to this question is yes	

Follow up questions from question 3a
ASK ONLY IF UNCERTAIN OR WANT TO GET BETTER PICTURE OF DEPRESSIVE STATE

During this time when you had worst two weeks where you felt sad, miserable or depressed….

How was your appetite?	(check for weight loss/gain)	
How was your sleep pattern?	(check if slept too much or trouble falling asleep or erratic sleep pattern)	
Nearly every day, were you unable to make up your mind about things you ordinarily would have had no trouble deciding about?		
Did you lack in energy or feel much more tired than usual even if you had not been working very hard?		
Did you feel worthless nearly every day?		
Did you think a lot about your own death, or someone else's death or death in general?		

Appendix 2: Telephone screening- Clinical subjects

Participant Checklist: Exclusion/Inclusion criteria to be checked over the telephone

****CONFIDENTIAL****

Question	Guidance	Answer (Y/N) and notes
1. Have you been diagnosed with a personality disorder? When?		
2. Have you been diagnosed with ADHD? When?		
3. Are you currently taking medication? • What medication are you taking and how many mg a day? • How long have you been taking this?	Exclude if on medication prescribed for a comorbid disorder apart from antidepressants	
4. Have you EVER had any other problems that have troubled you with regards to your mental health (apart from ADHD or BPD)?		
5. Have you ever had distinct episodes of depression or sadness different from what you're normally like lasting a week or more? **If no – go to Q 8**	**If all the time, then skip to Q7**	
6. Have you had a period **recently** where you felt sad, depressed, empty or tearful **nearly every day for at least 2 weeks**? If yes: • Did you lose all interest in things, or got no pleasure from things which would usually make you happy? • When did you first feel like this? • Are you still feeling like this?	If answer to **Q6** is yes, try to gauge severity of depressed episode using additional questions (below). Exclude if currently experiencing a **distinct episode** of depression	
7. Have you had more than one spell like this in the last 2 years? I mean more than just one period when you have been seriously depressed or anxious.	Consider excluding if depression is recurrent	
8. Have you had periods of feeling far more happy or energetic than your usual self, lasting for a week or more? So that your friends told you were talking too fast or that you were too 'hyper, compared to usual? If so, when was this?	Exclude if participant has experienced distinct episodes of mania/elation but not rapid cycling	
9. How often do you have a drink containing alcohol? (Never, Monthly or less, 2-4 times per month, 2-3 times per week, 4+ times per week)		
10. Approximately how many units of alcohol do you drink per day? **To calculate:** • Single shot is 1 unit • Alcopop is 2 Units • Can/pint of light beer is 1 unit. • Can/pint of lager is 2 Units • Can/pint of extra strong lager is 4 units • Party cocktail is 5 units • Glass of wine (175ml) is 2 units	Recommended limit for women 2-3 Units, for men 3-4 Units.	

11. Do you take any other drugs, legal or illegal? Which ones do you take? And how often do you take these? (prescribed or over the counter medications, cannabis (marijuana, hash), solvents, tranquilizers (Valium), barbiturates, cocaine, stimulants (speed), hallucinogens (LSD) or narcotics (heroin)		
12. Have you ever been addicted or dependent on any drugs or alcohol? If so, when was this?	Exclude if major history of drug or alcohol addiction, exclude if current substance abuse or addiction	
13. Have you ever suffered any injury to your head? If yes have you recovered from this/has it affected you in the long-term? Have you suffered from any neurological disorder (e.g. epilepsy, stroke or dementia)?	Exclude if they feel this has affected them in the long-term (e.g. if symptoms began from the injury). Exclude if answer to this question is yes	

Follow up questions from question 6

ASK ONLY IF UNCERTAIN OR WANT TO GET BETTER PICTURE OF DEPRESSIVE STATE

During this time when you had worst two weeks where you felt sad, miserable or depressed…

How was your appetite?	(check for weight loss/gain)	
How was your sleep pattern?	(check if slept too much or trouble falling asleep or erratic sleep pattern)	
Nearly every day, were you unable to make up your mind about things you ordinarily would have had no trouble deciding about?		
Did you lack in energy or feel much more tired than usual even if you had not been working very hard?		
Did you feel worthless nearly every day?		
Did you think a lot about your own death, or someone else's death or death in general?		

Appendix 3: Affective Lability Scale- short form (ALS-SF)

Please complete these questions reflecting how well these questions describe how you have been feeling over the **past week.** Please tick one box for each question.

		Very undescriptive	**Rather undescriptive**	**Rather descriptive**	**Very descriptive**
1	At times I feel just as relaxed as everyone else and then within minutes I become so nervous that I feel light-headed and dizzy.	❒	❒	❒	❒
2	There are times when I have very little energy and then just afterwards I have about the same energy level as most people.	❒	❒	❒	❒
3	One minute I can be feeling OK and then the next minute I'm tense, jittery, and nervous.	❒	❒	❒	❒
4	I frequently switch from being able to control my temper very well to not being able to control it very well at all.	❒	❒	❒	❒
5	Many times I feel nervous and tense and then I suddenly feel very sad and down.	❒	❒	❒	❒
6	Sometimes I go from feeling extremely anxious about something to feeling very down about	❒	❒	❒	❒
7	I shift back and forth from feeling perfectly calm to feeling uptight and nervous.	❒	❒	❒	❒
8	There are times when I feel perfectly calm one minute and then the next minute the least little thing makes me furious.	❒	❒	❒	❒
9	Frequently, I will be feeling OK but then I suddenly get so mad that I could hit something.	❒	❒	❒	❒
10	Sometimes I can think clearly and concentrate well one minute and then the next minute I have a great deal of difficulty concentrating and thinking clearly.	❒	❒	❒	❒
11	There are times when I am so mad that I can barely stop yelling and other times shortly afterwards when I wouldn't think of yelling at all.	❒	❒	❒	❒

12	I switch back and forth between being extremely energetic and having so little energy that it's a huge effort just to get where I am going.	❒	❒	❒	❒
13	There are times when I feel absolutely wonderful about myself but soon afterwards I often feel that I am just about the same as everyone else.	❒	❒	❒	❒
14	There are times when I'm so mad that my heart starts pounding and/or I start shaking and then shortly afterwards I feel quite relaxed.	❒	❒	❒	❒
15	I shift back and forth between being very unproductive and being just as productive as everyone else.	❒	❒	❒	❒
16	Sometimes I feel extremely energetic one minute and then the next minute I might have so little energy that I can barely do a thing.	❒	❒	❒	❒
17	There are times when I have more energy than usual and more than most people and then soon afterwards I have about the same energy level as everyone else.	❒	❒	❒	❒
18	At times I feel that I'm doing everything at a very slow pace but then soon afterwards I feel that I'm no more slowed down than anyone else.	❒	❒	❒	❒

Appendix 4: Affective Reactivity Index (ARI)

For each item, please mark the box for Not True, Somewhat True or Certainly True.
In the *last six months* and compared to others of the same age, how well does each of the following statements describe your behavior/feelings? Please try to answer all questions.

	NOT TRUE	SOMEWHAT TRUE	CERTAINLY TRUE
I am easily annoyed by others	☐	☐	☐
I often lose my temper	☐	☐	☐
I stay angry for a long time	☐	☐	☐
I am angry most of the time	☐	☐	☐
I get angry frequently	☐	☐	☐
I lose my temper easily	☐	☐	☐
Overall, my *irritability* causes me problems.	☐	☐	☐

Appendix 5: The Wender-Reimherr Adult Attention Deficit Disorder Scale-Emotional dysregulation subscale (WRAADDS-EDS)

The individual questions should be followed by general probes:

Has this occurred in the last week?
Have others commented about this?
What have they said?
What difficulties or problems has this caused with other people or work?

The individual items should be rated as follows:

0 – None, not present
1 – Mild, somewhat or sometimes true
2 – Clearly present or often true

The summary scores should be based on the ratings of the specific questions, together with any other symptoms in the area reported by the subject. The summary score should not be a simple average of the individual ratings. ~If only one question group is rated as clearly as present, a rating of "4" might be appropriate if this one factor is causing significant problems.

Summary ratings:

0- None
1- Mild
2- Moderate
3- Quite a bit
4- Very much

---

1. Temper

Do you frequently feel **irritable** or angry with your spouse, children, or other family members or at work, driving, or in other situations?	0	1	2
Do you have **angry outbursts** or lose your temper easily? Do you have a 'short fuse' or a 'low boiling point'?	0	1	2
Does your temper cause problems for you? Do you **lose control** during temper outbursts? (saying things you regret, becoming aggressive, acting in a threatening manner, or behaving impulsively)	0	1	2

Temper Summary Rating 0-4:

---

2. Affective Lability

Prior to scoring this question, the rater must differentiate between a major mood disorder and the lability of mood in subjects with ADHD. ADHD related dysphoria is generally brief, lasting hours, and usually has an identifiable precipitant. The exception is when the subject experiences persistent life problems (often self-produced), when the period of dysphoria may be extended. Similarly, distinguish between excitement (which may be mild) and over-enthusiasm from mood elevation with a manic quality.

AHDH clients may be comorbid for a major depression. Determine duration and frequency of episodes and presence of somatic concomitants to help distinguish discouragement, moodiness, and demoralization found in ADHD from major depression with its loss of interest and loss of the ability to experience pleasure.

Does your mood change frequently, going up and down - like a rollercoaster in the sense of getting sad or feeling 'up'?	0	1	2
Do you often have periods of being sad, blue, or discouraged? During these periods, are you overly self-critical or down on yourself?	0	1	2
Do you often feel **bored**? Do you easily lose interest in things?	0	1	2
Do you have periods of being excessively active, hyper, getting too excited, going too fast, or talking too much?	0	1	2

Affective Lability Summary Rating 0-4:

---

3. Emotional Over-Reactivity

Do you easily get feelings of being **overwhelmed**? Do you frequently feel 'hassled', frustrated?	0	1	2
Do you **overreact** to pressure, blow things out of proportion? Do small problems seem too difficult; do you 'make mountains out of molehills'?	0	1	2
When these reactions occur, do you have difficulties in managing tasks or getting things done? With pressures or stresses, do you become anxious, disorganized or confused?	0	1	2

Emotional Over-Reactivity Summary Rating 0-4:

Appendix 6: Mind Excessively Wandering Scale (MEWS)

How true is this statement for you?

Items:		Not at all or rarely	Some of the time	Most of the time	Nearly all the time or constantly
1.	I have difficulty controlling my thoughts	0	1	2	3
2.	I find it hard to switch my thoughts off	0	1	2	3
3.	I have two or more different thoughts going on at the same time	0	1	2	3
4.	My thoughts are disorganised and 'all over the place'	0	1	2	3
5.	My thoughts are 'on the go' all the time	0	1	2	3
6.	Because my mind is 'on the go' at bedtime, I have difficulty falling off to sleep	0	1	2	3
7.	I experience ceaseless mental activity	0	1	2	3
8.	I find it difficult to think about one thing without another thought entering my mind	0	1	2	3
9.	I find my thoughts are distracting and prevent me from focusing on what I am doing	0	1	2	3
10.	I try to distract myself from my thoughts by doing something else or listening to music	0	1	2	3
11.	I have difficulty slowing my thoughts down and focusing on one thing at a time	0	1	2	3
12.	I find it difficult to think clearly, as if my mind is in a fog	0	1	2	3
13.	I find myself flitting back and forth between different thoughts	0	1	2	3
14.	I use alcohol or other drugs to slow down my thoughts and stop constant 'mental chatter'	0	1	2	3
15.	I can only focus my thoughts on one thing at a time with considerable effort	0	1	2	3

Appendix 7: Weiss Functional Impairment Rating Scale-Self-report (WFIRS-S)

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Patient Name _____ Date _____ Date of Birth _____

Sex: ☐ Male ☐ Female Work: ☐ Full-time ☐ Part-time ☐ Other _____ School: ☐ Full-time ☐ Part-time

A. FAMILY	Never or Not at All	Sometimes or Somewhat	Often or Much	Very Often or Very Much	Not Applicable
1. having problems with family	0	1	2	3	☐
2. having problems with spouse/partner	0	1	2	3	☐
3. relying on others to do things for you	0	1	2	3	☐
4. causing fighting in the family	0	1	2	3	☐
5. makes it hard for the family to have fun together	0	1	2	3	☐
6. problems taking care of the family	0	1	2	3	☐
7. problems balancing your needs against those of your family	0	1	2	3	☐
8. problems losing control with family	0	1	2	3	☐

B. WORK					
1. problems performing required duties	0	1	2	3	☐
2. problems with getting your work done efficiently	0	1	2	3	☐
3. problems with your supervisor	0	1	2	3	☐
4. problems keeping a job	0	1	2	3	☐
5. getting fired from work	0	1	2	3	☐
6. problems working in a team	0	1	2	3	☐
7. problems with your attendance	0	1	2	3	☐
8. problems with being late	0	1	2	3	☐
9. problems taking on new tasks	0	1	2	3	☐
10. problems working to your potential	0	1	2	3	☐
11. poor performance evaluations	0	1	2	3	☐

C. SCHOOL					
1. problems taking notes	0	1	2	3	☐
2. problems completing assignments	0	1	2	3	☐
3. problems getting your work done efficiently	0	1	2	3	☐
4. problems with teachers	0	1	2	3	☐
5. problems with school administrators	0	1	2	3	☐
6. problems meeting minimum requirements to stay in school	0	1	2	3	☐
7. problems with attendance	0	1	2	3	☐
8. problems with being late	0	1	2	3	☐
9. problems taking on new tasks	0	1	2	3	☐
10. problems working to your potential	0	1	2	3	☐
11. problems with inconsistent grades	0	1	2	3	☐

D. LIFE SKILLS	Never or Not at All	Sometimes or Somewhat	Often or Much	Very Often or Very Much	Not Applicable
1. excessive or inappropriate use of internet, video games or TV	0	1	2	3	☐
2. problems keeping an acceptable appearance	0	1	2	3	☐
3. problems getting ready to leave the house	0	1	2	3	☐
4. problems getting to bed	0	1	2	3	☐
5. problems with nutrition	0	1	2	3	☐
6. problems with sex	0	1	2	3	☐
7. problems with sleeping	0	1	2	3	☐
8. getting hurt or injured	0	1	2	3	☐
9. avoiding exercise	0	1	2	3	☐
10. problems keeping regular appointments with doctor/dentist	0	1	2	3	☐
11. problems keeping up with household chores	0	1	2	3	☐
12. problems managing money	0	1	2	3	☐

E. SELF-CONCEPT					
1. feeling bad about yourself	0	1	2	3	☐
2. feeling frustrated with yourself	0	1	2	3	☐
3. feeling discouraged	0	1	2	3	☐
4. not feeling happy with your life	0	1	2	3	☐
5. feeling incompetent	0	1	2	3	☐

F. SOCIAL					
1. getting into arguments	0	1	2	3	☐
2. trouble cooperating	0	1	2	3	☐
3. trouble getting along with people	0	1	2	3	☐
4. problems having fun with other people	0	1	2	3	☐
5. problems participating in hobbies	0	1	2	3	☐
6. problems making friends	0	1	2	3	☐
7. problems keeping friends	0	1	2	3	☐
8. saying inappropriate things	0	1	2	3	☐
9. complaints from neighbors	0	1	2	3	☐

G. RISK	Never or Not at All	Sometimes or Somewhat	Often or Much	Very Often or Very Much	Not Applicable
1. aggresivse driving	0	1	2	3	☐
2. doing other things while driving	0	1	2	3	☐
3. road rage	0	1	2	3	☐
4. breaking or damaging things	0	1	2	3	☐
5. doing things that are illegal	0	1	2	3	☐
6. being involved with the police	0	1	2	3	☐
7. smoking cigarettes	0	1	2	3	☐
8. smoking marijuana	0	1	2	3	☐
9. drinking alcohol	0	1	2	3	☐
10. taking "street" drugs	0	1	2	3	☐
11. sex without protection (birth control, condom)	0	1	2	3	☐
12. sexually inappropriate behavior	0	1	2	3	☐
13. being physically aggressive	0	1	2	3	☐
14. being verbally aggressive	0	1	2	3	☐

Appendix 8: Childhood Trauma Questionnaire (CTQ)

When I was growing up ...	Never True	Rarely True	Sometimes True	Often True	Very Often True
1. I didn't have enough to eat.	●	●	●	●	●
2. I knew that there was someone to take care of me and protect me.	●	●	●	●	●
3. People in my family called me things like "stupid," "lazy," or "ugly."	●	●	●	●	●
4. My parents were too drunk or high to take care of the family.	●	●	●	●	●
5. There was someone in my family who helped me feel that I was important or special.	●	●	●	●	●
6. I had to wear dirty clothes.	●	●	●	●	●
7. I felt loved.	●	●	●	●	●
8. I thought that my parents wished I had never been born.	●	●	●	●	●
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	●	●	●	●	●
10. There was nothing I wanted to change about my family.	●	●	●	●	●
11. People in my family hit me so hard that it left me with bruises or marks.	●	●	●	●	●
12. I was punished with a belt, a board, a cord, or some other hard object.	●	●	●	●	●
13. People in my family looked out for each other.	●	●	●	●	●
14. People in my family said hurtful or insulting things to me.	●	●	●	●	●
15. I believe that I was physically abused.	●	●	●	●	●
16. I had the perfect childhood.	●	●	●	●	●
17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor.	●	●	●	●	●
18. I felt that someone in my family hated me.	●	●	●	●	●
19. People in my family felt close to each other.	●	●	●	●	●
20. Someone tried to touch me in a sexual way, or tried to make me touch them.	●	●	●	●	●
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	●	●	●	●	●
22. I had the best family in the world.	●	●	●	●	●
23. Someone tried to make me do sexual things or watch sexual things.	●	●	●	●	●
24. Someone molested me.	●	●	●	●	●
25. I believe that I was emotionally abused.	●	●	●	●	●
26. There was someone to take me to the doctor if I needed it.	●	●	●	●	●
27. I believe that I was sexually abused.	●	●	●	●	●
28. My family was a source of strength and support.	●	●	●	●	●

Appendix 9: Brief Symptom Inventory (BSI)

For each one, please tell me **how much that problem has bothered or distressed you <u>during the past week, including today</u>**. Please tell me whether each problem has bothered you not at all, a little bit, moderately, quite a bit, or extremely.

DURING THE PAST 7 DAYS, how much were you distressed by:	**Not at all**	**A little bit**	**Moderately**	**Quite a bit**	**Extremely**
1. Nervousness or shakiness inside	0	1	2	3	4
2. Faintness or dizziness	0	1	2	3	4
3. The idea that someone else can control your thoughts	0	1	2	3	4
4. Feeling others are to blame for most of your troubles	0	1	2	3	4
5. Trouble remembering things	0	1	2	3	4
6. Feeling easily annoyed or irritated	0	1	2	3	4
7. Pains in the heart or chest	0	1	2	3	4
8. Feeling afraid in open spaces	0	1	2	3	4
9. Thoughts of ending your life	0	1	2	3	4
10. Feeling that most people cannot be trusted	0	1	2	3	4
11. Poor appetite	0	1	2	3	4
12. Suddenly scared for no reason	0	1	2	3	4
13. Temper outbursts that you could not control	0	1	2	3	4
14. Feeling lonely even when you are with people	0	1	2	3	4
15. Feeling blocked in getting things done	0	1	2	3	4
16. Feeling lonely	0	1	2	3	4
17. Feeling blue	0	1	2	3	4
18. Feeling no interest in things	0	1	2	3	4
19. Feeling fearful	0	1	2	3	4
20. Your feelings being easily hurt	0	1	2	3	4
21. Feeling that people are unfriendly or dislike you	0	1	2	3	4
22. Feeling inferior to others	0	1	2	3	4
23. Nausea or upset stomach	0	1	2	3	4
24. Feeling that you are watched or talked about by others	0	1	2	3	4
25. Trouble falling asleep	0	1	2	3	4
26. Having to check and double check what you do	0	1	2	3	4
27. Difficulty making decisions	0	1	2	3	4

28. Feeling afraid to travel on buses, subways, or trains	0	1	2	3	4
29. Trouble getting your breath	0	1	2	3	4
30. Hot or cold spells	0	1	2	3	4
31. Having to avoid certain things, places, or activities because they frighten you	0	1	2	3	4
32. Your mind going blank	0	1	2	3	4
33. Numbness or tingling in parts of your body	0	1	2	3	4
34. The idea that you should be punished for your sins	0	1	2	3	4
35. Feeling hopeless about the future	0	1	2	3	4
36. Trouble concentrating	0	1	2	3	4
37. Feeling weak in parts of your body	0	1	2	3	4
38. Feeling tense or keyed up	0	1	2	3	4
39. Thoughts of death or dying	0	1	2	3	4
40. Having urges to beat, injure, or harm someone	0	1	2	3	4
41. Having urges to break or smash things	0	1	2	3	4
42. Feeling very self-conscious with others	0	1	2	3	4
43. Feeling uneasy in crowds	0	1	2	3	4
39. Thoughts of death or dying	0	1	2	3	4
40. Having urges to beat, injure, or harm someone	0	1	2	3	4
41. Having urges to break or smash things	0	1	2	3	4
42. Feeling very self-conscious with others	0	1	2	3	4
43. Feeling uneasy in crowds	0	1	2	3	4
44. Never feeling close to another person	0	1	2	3	4
45. Spells of terror or panic	0	1	2	3	4
46. Getting into frequent arguments	0	1	2	3	4
47. Feeling nervous when you are left alone	0	1	2	3	4
48. Others not giving you proper credit for your achievements	0	1	2	3	4
49. Feeling so restless you couldn't sit still	0	1	2	3	4
50. Feelings of worthlessness	0	1	2	3	4
51. Feeling that people will take advantage of you if you let them	0	1	2	3	4
52. Feeling of guilt	0	1	2	3	4
53. The idea that something is wrong with your mind	0	1	2	3	4

Appendix 10: Alcohol and Drug use

Alcohol Use Disorders Identification Test (AUDIT-C)

Questions	Scoring system					Your score
	0	1	2	3	4	
How often do you have a drink containing alcohol?	Never	Monthly or less	2 - 4 times per month	2 - 3 times per week	4+ times per week	
How many units of alcohol do you drink on a typical day when you are drinking?	1 -2	3 - 4	5 - 6	7 - 9	10+	
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	

Questions	Scoring system					Your score
	0	1	2	3	4	
How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
Have you or somebody else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?	No		Yes, but not in the last year		Yes, during the last year	

Substance use checklist (SUC)

Substance use checklist

For each drug listed, please tick the box under the category that best describes your use pattern in the past 1 year and circle ONE number in the last column best describing your reason of use of each drug.

		Never used	Several time a year	Several times a month	Several times a week	Daily	Several times a day	Reason of use
1	Alcohol							1 2 3
2	Marijuana or Hashish (e.g. cannabis, weed, skunk)							1 2 3
3	Ecstasy (e.g. MDMA)							1 2 3
4	Cocaine, street amphetamines, speed							1 2 3
5	Opiates (e.g. heroine, methadone, codeine)							1 2 3
6	Legal highs (e.g. spice)							1 2 3
7	OTHER DRUGS							1 2 3

1. Self-treatment, to reduce symptoms (e.g. reduces restlessness, anxiety, emotional instability, helps to sleep, and improves functioning
2. Recreational use (getting high, for fun, or for being part of a social group)
3. Other

Supplementary 4

A. Drug and Alcohol Use

The following two self-report measures were used to check for elevated drug and alcohol use and were not used as outcome measures in the analyses. Frequent alcohol use in the last 12 months (i.e. a score of 20 and above) was assessed by the AUDIT-C, an alcohol screen that can help identify individuals who are hazardous drinkers or have active alcohol use disorders (abuse or dependence). It was scored on a scale of 0 (no alcohol use) to 12 (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). Frequent drug use in the last 12 months (i.e. use of recreational drugs several times a week) was assessed by the Substance Use Checklist (SUC- Appendix 10), a short screen to identify patterns of illegal drug use in the past 12 months measured on a scale of 0 (never used) to 5 (several times a day). We identified five individuals from the clinical groups who reported elevated alcohol consumption. In addition, seven individuals of which one was a control subject, reported elevated substance use (i.e. legal highs, opiates, cocaine, and cannabis), and finally two clinical participants reported elevated substance and alcohol use.

We run sensitivity analyses on the main outcomes of MW measured by ESM and retrospective rating scale after removing the above-mentioned 14 participants. Overall key findings were not altered by excluding these individuals, and we can therefore assume results were not driven by these cases. Regarding MW intensity while controlling for anxiety and depression, sensitivity analyses no longer showed the significant differences between ADHD and BPD diagnoses our models revealed by including the individuals with elevated use of drug and alcohol. These results should be interpreted with a pinch of salt; with an even smaller sample size, the models might not have enough power to detect small effect sizes. Moreover, the significance values of the models before and after the sensitivity analyses only marginally changed from being nearly significant to not.

B. Correlations of the MW Items

Table 1 Correlations of the multiple MW measures all significant at the .01 level (2-tailed)

	Item-1	Item-2	Item-3	Item-4	Item-5
Item-1		.901	.883	.876	.812
Item-2	.901		.971	.951	.903
Item-3	.883	.971		.957	.930
Item-4	.876	.951	.957		.946
Item-5	.812	.903	.930	.946	

C. Multilevel Models for MW Intensity- ADHD*BPD Interactions

Table 2 Type III tests of fixed effects

	Unadjusted model				Adjusted model for anxiety and depression			
	Num DF	Den DF	F value	*p* value	Num DF	Den DF	F value	*p* value
Item-1	1	93.99	10.94	**.001**	1	93.24	9.16	**.003**
Item-2	1	93.81	10.70	**.001**	1	92.28	8.74	**.004**
Item-3	1	94.21	14.60	**<.001**	1	92.13	11.92	**<.001**
Item-4	1	93.93	21.70	**<.001**	1	91.77	20.03	**<.001**
Item-5	1	93.92	16.69	**<.001**	1	91.02	15.09	**<.001**

D. Estimated Means for MW Intensity Models

Table 3 Estimated means from multilevel models of MW intensity adjusted for anxiety and depression

Estimated Means	No diagnosis	ADHD diagnosis	BPD diagnosis	Comorbid ADHD/BPD diagnosis
Item-1	35.47	53.97	47.69	46.90
Item-2	36.15	56.02	41.96	42.90
Item-3	37.07	59.18	42.70	41.59
Item-4	33.29	61.30	46.71	46.75
Item-5	28.11	59.35	46.10	48.20

Inspection of the interactions and the estimated means showed a consistent pattern. The effects of ADHD and BPD were not additive. While we found differences between controls and all clinical diagnosis groups, the highest MW intensity was found for the ADHD diagnosis, whereas BPD and the comorbid ADHD/BPD

diagnosis group were comparable. The effect of an ADHD diagnosis seems to depend on the presence of a BPD diagnosis.

E. Multilevel models for MW instability

Table 4 Between-diagnoses differences on MW instability as estimated by multilevel modelling

Instability	Model parameters for group	ADHD diagnosis vs BPD diagnosis	ADHD diagnosis vs ADHD/BPD comorbid diagnosis	BPD diagnosis vs comorbid ADHD/BPD diagnosis
Item-1	Estimate S.E *p* value	.16 .30 1	.06 .28 1	-.10 .31 1
Item-2	Estimate S.E *p* value	.10 .32 1	.10 .30 1	.005 .33 1
Item-3	Estimate S.E *p* value	.18 .29 1	-.01 .28 1	-.19 .31 1
Item-4	Estimate S.E *p* value	-.01 .30 1	.09 .29 1	.10 .32 1
Item-5	Estimate S.E *p* value	-.06 .37 1	-.06 .35 1	.005 .39 1

F. Cross-validation between the MEWS and ESM measures of MW

Using Pearson correlations, we cross-validated ambulatory assessments of MW with retrospective self-report measures of MW (the MEWS) to examine the strength of association between these measures and establish whether the scale reflects the same construct as the ESM data. To control for confounding effects of potential comorbid anxiety and depression, we first examined if the measures of interest correlated with these covariates, and if so controlled for these in correlation analyses using partial correlations.

Anxiety and depression were significantly and moderately correlated with retrospective and ESM ratings of MW (Pearson's r between .5 and .7) and were therefore partialled out in the below analyses. Partial correlations between mean ratings of MW from ESM assessments and total scores obtained from the MEWS confirmed significant moderate to strong associations between the two measures (see Table 5).

Supplementary 4

Table 5 Correlation coefficients for relationship between MEWS total scores and mean intensity of MW from ESM data

MEWS total scores	Mean_Item1	Mean_Item2	Mean_Item3	Mean_Item4	Mean_Item5
(ρ) partial correlation adjusted for anxiety and depression	.40*	.45*	.49*	.55*	.53*
Bivariate correlation unadjusted for anxiety and depression	.59*	.65*	.66*	.74*	.72*

*. Correlations significant at the 0.01 level (2-tailed)

Supplementary 5

A. Drug and alcohol use

Frequent alcohol and drug use in the last 12 months were assessed by the Alcohol Use Disorders Identification Test and the Substance Use Checklist respectively (see section 2.4.1.6 in chapter 2 for details on the measures). Five individuals from the clinical groups were identified as reporting elevated alcohol consumption. In addition, seven individuals of which one was a control subject, reported elevated substance use (i.e. legal highs, opiates, cocaine, and cannabis), and finally two clinical participants reported elevated substance and alcohol use.

Sensitivity analyses were conducted on the main outcomes of emotional dysregulation measured by ESM and retrospective rating scales after removing the above-mentioned 14 participants. Findings from the ESM data were not altered by excluding these individuals, and we can therefore assume ESM results were not driven by these cases.

Regarding retrospective self-report measures of emotional dysregulation (ALS-SF and WRAADDS-EDS), findings revealed that in addition to the significant case-control differences (similar to findings for the tests without excluding the 14 individuals), all three clinical groups also significantly differed from one another ($p<.001$) on both scales, with the ADHD group reporting lower scores compared to the BPD group, who also reported lower scores than the comorbid ADHD/BPD group.

B. ROC analyses

The sensitivity of emotional dysregulation measures for predicting ADHD and BPD diagnostic accuracy were examined by applying receiver operating characteristic (ROC) analysis to the individual data of participants, with diagnosis as the state variable and emotional dysregulation as the independent variable (see Table 1). ROC analysis for predicting BPD diagnosis by retrospective emotional dysregulation measures showed marginally better but non-significant predictive ability (ranging between .83 and .88) than for predicting ADHD diagnosis (ranging between .74 and .82).

Table 1 Discriminatory accuracy of ADHD and BPD diagnosis on symptoms of emotional dysregulation estimated by the area under the receiver operating characteristic curve (AUC)

	ADHD AUC (95% CI)	BPD AUC (95% CI)
ALS-SF	.80 (.71-.88)	.83 (.76-.90)
WRAADDS-EDS	.82 (.74-.90)	.88 (.82-.94)