Examining psychobiological mechanisms underlying bipolar spectrum disorder symptom presentation.

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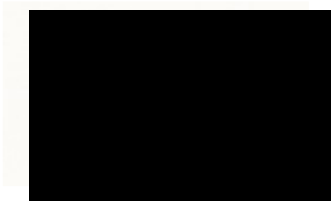
Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

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Overview

This thesis examines the psychobiological mechanisms underlying bipolar spectrum disorder mood symptom presentation in two parts: dysregulation in short-term affective processes (Part one), and dysregulation in reward processing (Part two).

Part one presents a systematic review, which sought to identify convergence of findings from studies using ecological momentary assessment/experience sampling (EMA/ESM) methodology to examine affect dynamics in bipolar spectrum disorder, unipolar depression and borderline personality disorder populations. 38 studies using EMA/ESM methodology to examine affect dynamics across clinical groups and healthy controls were included. Findings showed that altered affect dynamics were identified across all disorders in comparison to healthy controls. Findings suggest that the degree of affect dysregulation may differentiate clinical groups.

Part two presents an empirical study, which sought to examine the relationship between reward processing and subthreshold BSD symptoms longitudinally in a large community-based sample, using a monetary incentive delay functional magnetic resonance paradigm. Region-of-interest analyses in the ventral striatum were conducted to examine how neural activation during anticipation of rewards at 14 was related to mood symptoms at 14 and 22 years. Although no association was observed between neural activation and mood symptoms at baseline, enhanced sensitivity to anticipation of rewards, reflected in higher levels of neural activation, at age 14 predicted lower levels of (hypo)manic symptoms at age 22.

Part three comprises a critical appraisal of the research process. This includes reflections on the author's positionality and influences on the research, the challenges of

neuroimaging research, and the value of understanding the neurobiological mechanisms underlying psychopathology.

Impact Statement

Bipolar spectrum disorder (BSD) is known as a chronic, debilitating disorder that causes considerable disease and economic burden. BSD is often misdiagnosed initially due to the overlap of some of its symptom constructs and high comorbidity rates with other forms of psychopathology such as unipolar depression, substance use disorders or schizophrenia (Matza et al., 2005; Meyer & Meyer, 2009; Mitchell et al., 2010). Misdiagnosis can have harmful consequences and has been associated with a more severe and chronic progression (Stensland et al., 2008, 2010). Thus, research that aims to identify markers that confer vulnerability specifically for BSD and which could facilitate early, and accurate diagnosis are crucial.

The findings from the systematic review of studies using ecological momentary assessment/experience sampling methodology to examine patterns of short-term affect dynamics across various psychiatric disorders represent an important step towards identifying dysregulated affective processes that are transdiagnostic versus those that are unique to BSD. This study is the first study to systematically compare patterns of dysregulated affect dynamics across BSD, unipolar depression, and borderline personality disorder and as such contributes to the wider evidence-base on the relationship between affect dynamics and psychopathology. Findings suggest that altered levels of affective dynamics, in particular dysregulation of negative affect, may represent transdiagnostic processes common to a variety of psychopathologies. Our findings prompt further research to examine whether there

are subtle differences across disorders in the dynamics of affective states of varying levels of valence, activation, and distress. Findings further indicate that dysregulated affective processes are clinically relevant to disorders in which clinical practice has not historically placed a high degree of emphasis on such processes, such as unipolar depression. This has important clinical considerations for the assessment and treatment of these disorders; attention to affect dynamics may provide a more nuanced clinical picture of an individual's presentation, their experience of triggers and stressors, and their subsequent use of coping strategies.

The findings from the empirical study represent an important step towards examining the relationship between subthreshold BSD mood symptoms and reward perception longitudinally. This is the first study to examine neural reward function as a predictor of later mood symptoms in a community-based sample. Our findings contribute to existing literature examining the neurobiological mechanisms that underlie BSD psychopathology. We observed an association between neural reward function and later mood symptoms that occurred in the opposite direction than was predicted in accordance with the prevailing model of BSD, the Reward Hypersensitivity Model (Nusslock & Alloy, 2017). Thus, our findings prompt further research to examine the role of reward hyposensitivity in conferring risk for BSD. Such research may facilitate the identification of neurobiological markers that may be correlated with behavioural indices and used to complement self-report based diagnostic approaches to facilitate early and accurate diagnosis. This is particularly relevant for BSD, where misdiagnosis and late diagnosis is common (Alloy et al., 2016). Furthermore, such neurobiological markers may provide more precise targets for therapeutic interventions and may additionally serve as indicators of treatment efficacy.

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Part 1: Literature Review

Patterns of short-term affect dynamics across mood disorders: a systematic review of ecological momentary assessment and experience sampling methodology studies

Abstract

Background: Dysregulated affect dynamics are a well-accepted facet of some psychopathologies e.g., borderline personality disorder (BPD). Advances in technology have enabled more fine-grained analysis of affect dynamics across different disorders; however, a coherent body of evidence comparing affect dynamic patterns across mood disorders is lacking.

Methods: A systematic review of PsychINFO, MEDLINE and Web of Science databases was undertaken, in addition to reference lists of included studies and relevant review articles. Searches were completed in April 2022. Selected studies used Ecological Momentary Assessment/Experience-Sampling to examine affect dynamics in individuals above 18-years old with a diagnosis of bipolar spectrum disorder (BSD), unipolar depression, or borderline personality disorder (BPD), and compared these groups to clinical and healthy controls. Given the variability of protocols employed across studies, results are discussed narratively rather than meta-analytically.

Results: The search identified 38 relevant studies. Considerable heterogeneity was observed across methodological approaches and EMA/ESM protocols. Heightened levels of variability and instability in negative affect were identified across all clinical groups in comparison to healthy controls. Degree of dysregulation in negative affect may discriminate between three clinical groups. Increased variability and instability in positive affect were identified in BPD and BSD, however, there were conflicting findings in unipolar depression.

Conclusions: Findings suggest that the clinical significance of altered affect dynamics extends beyond disorders in which it is a well-established trait. In particular, dysregulated levels of variability and instability of negative affect may represent transdiagnostic processes that have potential as investigational and therapeutic targets across various forms of psychopathology.

1. Introduction

1.1. Overview

Affect dysregulation has been described as a feature in a wide range of psychiatric disorders including bipolar spectrum disorder (BSD) and borderline personality disorder (BPD) (American Psychiatric Association, 2013). It has further been suggested that these disorders may be characterised by distinct patterns of affective dynamics that significantly deviate from the normal fluctuations that everyone experiences in their day-to-day life (Lamers et al., 2018). Affect dysregulation in these disorders has traditionally been diagnosed and characterised using clinical interview techniques that rely heavily on self-report (Broome et al., 2015). However, when an individual is asked to rate their mood over a certain time period, usually in the order of a week or two, they are required to perform several complex calculations such as estimating what their baseline affect has been, aggregate their affective states over time, and average over a range of affective states (Trull et al., 2015). Moreover, self-report data can be influenced by factors such as current mood state or cognitive styles, which is particularly relevant in the context of depression (Baltasar-Tello et al., 2018; Trull et al., 2015); recent evidence has suggested that individuals with depression display a negative bias in their self-report responses (Ben-Zeev et al., 2009). Additionally, self-report data typically assesses affect dynamics in the order of weeks, whereas the dynamic nature of affective processes may unfold over seconds, minutes, or hours (Broome et al., 2015; Dunster

et al., 2021). Recent advances in technology have facilitated the development of ambulatory assessment techniques such as ecological momentary assessment (EMA) and experience sampling methodology (ESM), which are capable of capturing moment-to-moment changes in affect in everyday life (Heininga & Kuppens, 2021). The use of these technologies has increased substantially in the past two decades and has been used to provide detailed characterisation of the affect dysregulation that occurs across different forms of psychopathology (Heininga & Kuppens, 2021; Houben et al., 2015). Whilst prior research has provided considerable insights on affect dynamics across BSD, unipolar depression (UD) and BPD samples, due to a number of challenges outlined below, a coherent body of evidence that explores patterns of affect dynamics across these disorders is lacking. Therefore, this systematic review aims to address this gap and further understanding of the patterns of affect dynamics and dysregulation across BSD, UD and BPD samples.

1.2. Mood Disorders

Mood disorders such as bipolar spectrum disorder (BSD) and unipolar depression (UD) are currently one of the most prevalent and debilitating group of mental disorders; they affect approximately ten percent of the population each year and they represent the leading cause of disability worldwide (World Health Organisation, 2017). This group of disorders causes substantial impairments in social and occupational functioning and a high risk of mortality among individuals suffering from these disorders, leading to a significant disease burden for both the individual and society as a whole, and representing a major public health problem (Romera et al., 2010; Rosa et al., 2010). Mood disorders are so named because their primary impact occurs on an individual's affective state. In other words, individuals diagnosed with a mood disorder experience distorted emotions and/or emotions that are inconsistent with

current context, to such an extent that it interferes with an individual's ability to function (Heininga & Kuppens, 2021). As a result, extant research and diagnostic processes for mood disorders have focused on the experience of affect, and how affective processing relates to psychological wellbeing. The majority of research to date has traditionally adopted a static understanding of emotions in which emotions are investigated as either single, monotone states that switch on and off in response to an external or internal event, or as traits that describe individuals in terms of their overall tendency to experience certain emotions (Houben et al., 2015). However, the functionality of emotional processing is dependent on its fundamentally dynamic nature; emotions alert us to salient changes in our environment and allow us to prepare to respond to these changes in adaptive and effective ways (Dejonckheere et al., 2019). Therefore, a static perspective of emotion processing ignores the moment-to-moment ebb and flow of emotions that may be triggered by various contextual factors (Trull et al., 2015). Patterns of emotional fluctuations contain important information about how an individual copes with changes in their environment and how they regulate their emotions (Larsen, 2000). Both contribute to psychological wellbeing and as such, investigating emotions from a dynamic perspective is a crucial avenue to explore in the context of mood disorders (Houben et al., 2015).

1.3. Affect Dynamics

Affect dynamics can be defined as the patterns and regularities that characterise changes and fluctuations in an individual's emotional and affective states over multiple points in time across seconds, hours or days (Kuppens, 2015). Consequently, investigating affect dynamics requires the measurement of affective states at multiple points in time and the generation of affective time series (Dejonckheere et al., 2019). Several different ways of

operationalising patterns of affect dynamics may be computed from the same affective time series data. The most common of these are measures of affective variability, instability, and inertia (Houben et al., 2015).

Measures of affective variability reflect the overall dispersion of an individual's scores across a sampling period (Crowe et al., 2019). An individual characterised by higher levels of affective variability would exhibit larger deviations from their average affective level and would therefore report more extreme levels of emotion (Houben et al., 2015). Affective variability is typically calculated as the within-person standard deviation or variance of affective states over time (Trull et al., 2015). Affective instability is conceptualised as the magnitude of changes in emotions from one moment to the next (Trull et al., 2015). An individual characterised by high levels of instability would report more frequent and intense shifts in emotions over time, resulting in a more unstable affective landscape (Houben et al., 2015). Affective instability is generally calculated as the mean successive squared difference (MSSD), the root mean successive squared difference (RMSSD), or the probability of acute changes (PAC) between consecutive emotion scores (Thompson et al., 2012). Affective instability can be thought of as conceptually related to affective variability; however, it additionally captures temporal dependency or the moment-to-moment consistency of emotion across adjacent measures (Trull et al., 2015). Affective inertia is defined as the extent to which emotions persist over time, or in other words, how well the intensity of an affective state can be predicted from the affective state at a previous time point (Thompson et al., 2012). High levels of affective inertia would result in emotions that are more self-predictive over time (Houben et al., 2015). This would reflect affective fluctuations that persist over time, showing limited return to baseline levels. Affective inertia is typically calculated as the autocorrelation of emotions across time (Trull et al., 2015).

A recent meta-analysis to address which affect dynamics metrics best predict psychopathology and wellbeing concluded that these metrics capture a negligible amount of variance in psychological wellbeing over and above mean levels of positive and negative affect, apart from affective variability (Dejonckheere et al., 2019). However, the authors note that by only examining mean levels of positive and negative affect, the meaningful fluctuations in an individual's affective life may be overlooked (Dejonckheere et al., 2019). Further, research that explores the association between affective processing and individual differences in psychological wellbeing does not explicate the possible dynamic processes that underlie psychopathology (Lapate & Heller, 2020). Therefore, despite the possibly limited predictive ability of measures of affect dynamics such as instability or inertia, they may provide insight into the potential mechanisms involved in psychopathology (Dejonckheere et al., 2019).

Empirical research on affect dynamics and their relationship with psychological wellbeing has exploded in the past three decades (Houben et al., 2015). This has been facilitated by technological advances that have aided the longitudinal assessment of emotions in individuals in their everyday lives. One such advancement has been the field of ecological momentary assessment (EMA) or experience sampling methodology (ESM), which provides multiple micro-assessments of affective experience across time and situations, enabling the examination of the dynamic nature of various affective processes that are theorised to be crucial in the development and trajectory of various psychiatric disorders (Trull et al., 2015).

1.4. Ecological Momentary Assessment (EMA) and Experience Sampling Methodology (ESM)

EMA and ESM are part of a larger group of methodologies known as ambulatory assessment methods (Vachon et al., 2018). They consist of structured diary techniques which

involve the collection of data on repeated occasions, in real time, and in the context of everyday life (Bell et al., 2017). In an EMA/ESM protocol, an electronic signalling device prompts individuals to complete particular measures multiple times a day, at fixed or random time points, and across multiple consecutive days (Heininga & Kuppens, 2021). These approaches began in the 1940's and were typically performed using pen and paper, requiring individuals to carry clinical research diaries around with them (Dunster et al., 2021). However, with the advancement of new technologies, EMA/ESM is now performed using personal handheld computers and smartphones (Sedano-Capdevila et al., 2021). EMA/ESM offers several benefits in comparison to laboratory-based assessments (Csikszentmihalyi & Larson, 2014; Ebner-Priemer et al., 2009; Reis & Gable, 2000). Firstly, EMA/ESM involves a naturalistic approach; individuals typically report on their subjective experiences in the context of the flow of their daily lives. This approach ensures the ecological validity of the data collected, enabling findings to be generalisable to outside of the laboratory (Heininga & Kuppens, 2021). Further, individuals are required to report on their experiences at the time of the signal; collecting data close to real-time weakens the potential influence of recall bias (Heller et al., 2019). Additionally, EMA/ESM approaches examine individuals' experiences in their usual surroundings, thereby enabling the identification of contextual factors that may potentially be influencing the psychological processes under investigation (Kwapil et al., 2011; Stange et al., 2018). Finally, EMA/ESM enables the collection of intensive longitudinal information about the real-time manifestations and interrelations among different facets of affective life (Heller et al., 2019). This consequently facilitates the testing of hypotheses relating to the patterns of affect dynamics and their relation to psychological wellbeing and psychopathology. The reliability, validity and feasibility of EMA/ESM has been demonstrated across a range of clinical and control samples (Dunster et al., 2021). Further, the application

of EMA/ESM methods has been used to identify the longitudinal trajectory of psychiatric disorders, describe real-time changes in psychiatric symptoms, identify cognitive, behavioural and affective patterns that discriminate between different clinical states, and provide psychological interventions (Baltasar-Tello et al., 2018).

1.5. Affect Dynamic Profiles in Mood Disorders

EMA/ESM methods have been employed to explore affective life in a variety of psychiatric disorders such as schizophrenia (Cho et al., 2017), psychosis (Bell et al., 2017), anxiety disorders (Bowen et al., 2006), personality disorders (Snir et al., 2017), unipolar depression (aan het Rot et al., 2012), and bipolar disorder (Merikangas et al., 2019). Findings from the past decade have revealed a strong association between greater variability and instability in negative affect and poor psychological wellbeing in general (Houben et al., 2015). Variability and instability in positive affect have also been shown to be positively related to poorer psychological health, however, this association appears to have less predictive power in comparison to the relationship between variability and instability in negative affect and psychological wellbeing (Heininga & Kuppens, 2021). In relation to mood disorders, findings have suggested a similar relationship between greater variability and instability in negative affect and poorer psychological wellbeing in depression (aan het Rot et al., 2012; Baltasar-Tello et al., 2018; Houben et al., 2015). However, no significant associations between variability and instability in positive affect and psychological wellbeing have been observed in depressed populations (Peeters et al., 2006; Thompson et al., 2012). Conversely, depression has actually been associated with less variability, though not instability, in positive affect (Houben et al., 2015). This may reflect the depressive symptom construct of anhedonia, which may result in blunted positive affect reactivity, contributing to decreased variability in positive

affect (Crowe et al., 2019). Increased affective instability has additionally been observed in BPD (Santangelo et al., 2014; Trull et al., 2008), anxiety disorders (Pfaltz et al., 2010), bulimia nervosa (Anestis et al., 2010), post-traumatic stress disorder (Kashdan et al., 2006), and BSD (Jones et al., 2005). Higher levels of affective variability have also been observed in BPD, however, it is unclear whether the increased variability and instability observed in BPD is specific to the disorder, or reflective of more transdiagnostic affective dysregulation, as heightened levels of variability and instability have also been observed in bipolar populations (Lamers et al., 2018). Higher levels of inertia, particularly for negative affect, have been observed in depression and associated with traits linked to increased vulnerability to depression, e.g., low self-esteem, neuroticism, rumination (Koval et al., 2012; Kuppens et al., 2010; Suls et al., 1998), and polymorphisms in the serotonin transporter (van Roekel et al., 2018).

1.6. Current Study

As highlighted above, there is a substantial evidence-base examining affect dynamics in mood disorders; however, there are marked methodological and measurement differences between studies, and studies examining differences in affect dynamics across different clinical groups is limited. Given these challenges, a coherent body of evidence comparing the patterns of affect dynamics across psychiatric disorders in general, and mood disorders in particular has not yet formed. Further, existing literatures examining the above parameters of affect dynamics in mood disorders are largely independent and as such, the nature of the relationship amongst these measures has not yet been fully examined. Illuminating the specific relationships between particular affect dynamic patterns and different forms of psychopathology would significantly increase our understanding of the patterns of affective

dysregulation that are involved in different psychiatric disorders. Further, this would facilitate the separation of transdiagnostic and distinct processes of affective dysregulation that are involved in psychological wellbeing and psychopathology. Increasing this understanding would significantly aid in the detection, diagnosis, prognosis, and treatment assessment purposes in this context (Houben et al., 2015).

The primary aims of this review are to address the abovementioned gaps and assist in providing insights towards the patterns of affect dynamics and dysregulation across mood disorders. We performed a systematic review to identify convergence of findings from EMA/ESM studies examining affect dynamics in bipolar disorder, unipolar depression and borderline personality disorder populations. Thus, this review aims to summarise evidence and describe the different patterns of short-term changes in affective experience that occur across three different psychiatric disorders. Such a review will facilitate the formulation of conclusions regarding the relationship between psychopathology and affect dynamics.

2. Methods

The present review followed recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for conducting systematic reviews (Moher et al., 2009). A systematic literature search was conducted on 14/04/2021 to identify studies using EMA/ESM methodology to explore short-term affect dynamics across affective disorders.

2.1. Search Strategy

Relevant studies were retrieved by searching Web of Science, Medline, and PsychInfo databases. These databases were chosen as they encompass literature from a wide range of fields, including healthcare, biomedical sciences, social sciences, and humanities. The search strategy combined synonymous terms relating to three key concepts of "short-term affect dynamics", "ecological momentary assessment", and "affective disorders". Terms relating to these key concepts were searched in titles, abstracts, and keywords within the three electronic databases. To reflect the fact that EMA was only added as an index term to PsychInfo and Medline databases in 2019, and that there exists a range of other techniques with a family resemblance to EMA/ESM, search terms were expanded to included keywords such as time series and event contingent sampling. Relevant MeSH terms (e.g., affective instability or Ecological Momentary Assessment), were used for PsychInfo and Medline databases. Further details about the database search strategy and search syntax are available in the Appendix A. Identified studies were imported into the referencing database, Rayyan QCRI (Ouzzani et al., 2016), and duplicates were systematically removed. The title and abstracts of each study were screened for basic criteria, and full texts were then independently evaluated against the exclusion and inclusion criteria. Reference lists of studies meeting inclusion criteria and of relevant review papers were cross-referenced to identify further relevant published studies. The literature search, screening, selection, and data extraction was conducted by the author. To investigate the reliability of the selection process, a second, independent rater judged the relevance of 374 (approximately 20%) of the original collection of 1874 articles based on inclusion and exclusion criteria. Interrater agreement was present for 99.1% of articles resulting in a Cohen's *k* equal to .087, indicating almost perfect

agreement. Differences in opinion were resolved by discussion with a third reviewer, the author's supervisor.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria were as follows:

1. The study was an original study published in a peer-reviewed journal;
2. The study was available in the English language;
3. Participants were over 18 years of age and were diagnosed as having the following disorders: bipolar spectrum disorder (BSD), unipolar depression (UD) or borderline personality disorder (BPD);
4. Standardised diagnostic criteria (either Diagnostic and Statistical Manual of Mental Disorders (DSM-5, APA, 2013) or Internal Diagnostic Criteria -10 (ICD-10)), were used to determine psychiatric diagnoses;
5. The study had a sample size of five participants or more;
6. The study employed EMA/ESM to explore short-term affect dynamics;
7. The study reported a measure of intraindividual affect dynamics based on at least three consecutive time points and a maximum interval of one day between consecutive measurements;
8. The study reported results for a statistical comparison of a measure of short-term affect dynamics: variability (within-person SD or variance), instability (MSSD, MASD, RMSSD), or inertia (autocorrelations or autoregressive slopes) between at least two groups or which one was BPD, BSD or UD;
9. The study reported self-reported data reflecting affective experience.

Exclusion criteria were as follows:

1. The study was a proof of concept, protocol for randomised clinical trial, case study, review, thesis or book chapter;
2. Participants under 18 years of age;
3. The study was not available in the English language;
4. The study evaluated mood states but did not include a psychiatric diagnosis.

2.3. Data Extraction

The author performed data extraction. The data extracted included basic study information, including author, year of publication and impact factor of journal in which the article appeared. We further extracted data relating to study aims, design, and sample characteristics including total sample size, primary diagnosis, comparison group, mean age, and gender. Data relating to the characteristics of EMA/ESM protocol was also extracted and this included modality, sampling rate, number of measurements per day, recording design and the measure of affect used, including information on the individual items and valence of the items assessed. Data relating to performance metrics were also extracted. This included retention rate, adherence rate, proportion of missing data, and how missing data was dealt with. Finally, we extracted data relating to the parameter of affect dynamics that were examined including measures of variability, instability, or inertia, statistical analyses employed to analyse the data and the main findings.

2.4. Analyses

A narrative synthesis of the findings was used in this study due to the broad nature and variability in the study identified.

3. Results

3.1. Results of the Search

Using the described search strategy, a total of 1374 prospective results were obtained from Web of Science, 699 from Medline, and 1030 from PsychINFO, yielding a total of 3103 results exported from the databases into the referencing database, Rayyan QCRI (Ouzzani et al., 2016). Duplicate search results were deleted using Rayyan. The titles and abstracts of 1873 remaining papers were then screened to identify studies to review, leaving 204 papers using EMA/ESM methodology to examine short-term affect dynamics in mood disorders. Following more detailed examination, a further 171 papers were omitted based on our selection criteria, leaving 33 eligible articles. Having examined reference lists of these eligible articles for additional studies meeting our selection criteria, five additional articles were identified. This yielded a final total of 38 studies included within this review (Figure 1).

3.2. Included Studies

38 studies met the inclusion criteria for the review. Publication dates for the included studies ranged between 1991 and 2021. Details of the key characteristics and main findings of each study are shown in Table 1. To aid readability, numbered referencing will be employed in the results section. Studies will be referenced in the text using numbers that correspond to the referred studies in Table 1. The EMA/ESM protocol and statistical procedures used varied considerably across the studies and thus, the statistics for the main findings are not presented. The majority of studies primarily focused on using EMA/ESM to examine differences in affect dynamics across different clinical groups and healthy controls[2-6, 8-10, 12-15, 17-18, 21-22, 24-29, 31-33, 35-37]. The remaining studies, primarily focused on using EMA/ESM to examine the relationship between affect dynamics and other variables across different clinical

groups and healthy controls[1, 7, 16, 19, 30, 34, 38]. Thirteen studies included investigations of affect dynamics with other factors as supplementary research questions[3-4, 10, 12-14, 18-19, 25-27, 30]. However, as the focus of this review was examining the patterns of affect dynamics across mood disorders, we will not review additional findings in-detail here. Significant findings and observations are noted within Appendix B. Briefly, additional concomitant research questions included examining the relationship between affect dynamics and other variables across different clinical groups and healthy controls and examining different affective phenomena including emotional switching[11], emotional reactivity[17]. Other variables included psychopathological symptoms[1, 9, 16, 14, 20], variables relating to cognition[1, 30], suicidality[4], tiredness[4], distress[6], sleep and related variables[7], temporal trends in affect dynamics[9], reward reactivity and recovery[10], occurrence of events and subjective affective reactivity to events[12, 18, 35], interpersonal variables[13, 14, 19, 23], energy[14], trait levels of positive and negative affect[15], blood pressure[16], impulsivity[14, 19], personality traits[19], self-esteem[4, 24, 27], age[25], resting state fMRI[30], speed of thought[14], and unity of self-concept[34].

Figure 1.

Prisma Flow Diagram of Systematic Selection Process (Adapted from Moher et al., 2009)

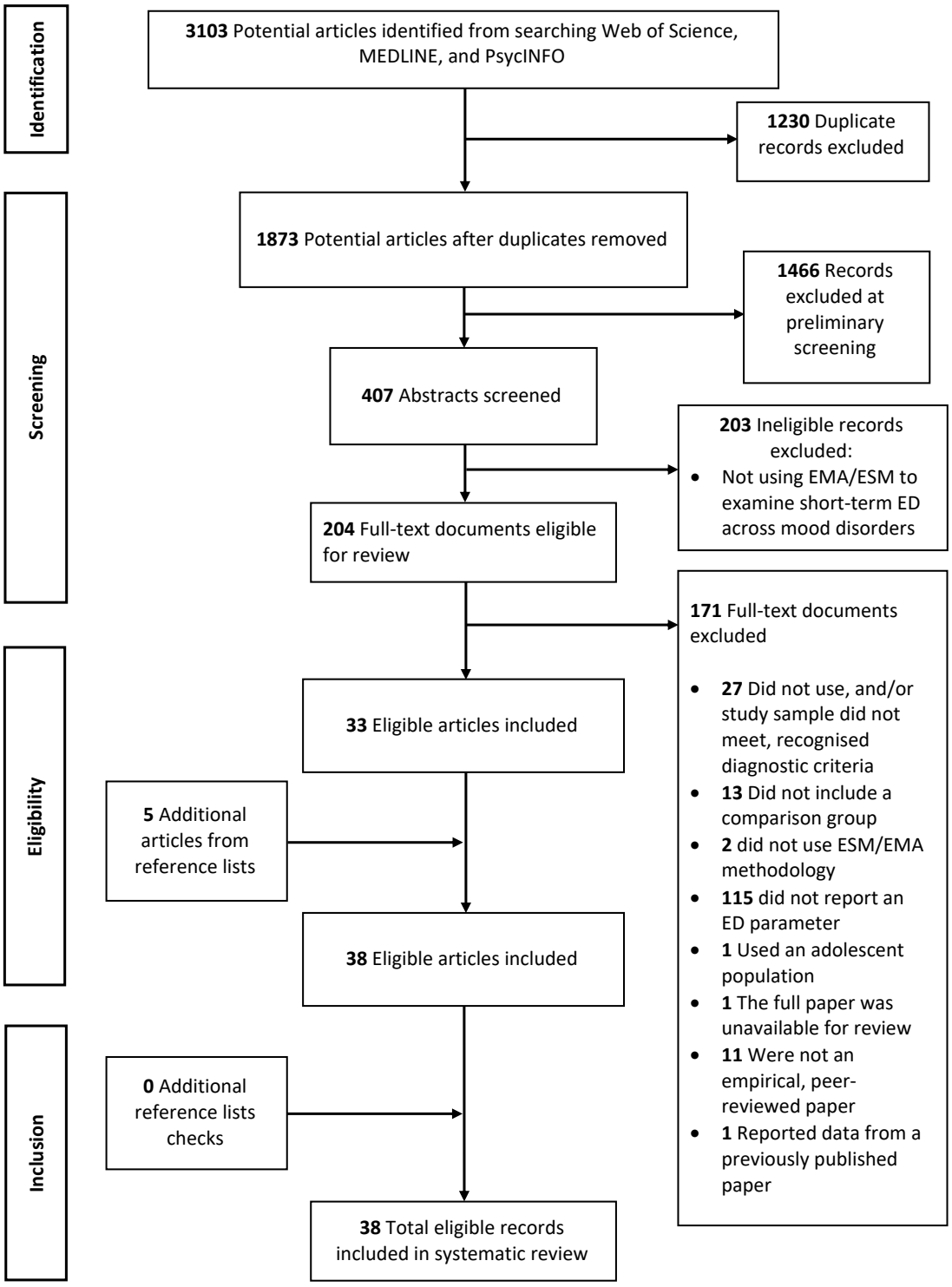

Table 1.

Included Studies: Key Characteristics and Main Findings

Study	Primary clinical group	Comparison group	Measure of Affect dynamics[a]	Main Findings
1. Bomyea et al. (2021)	BSD (*n* = 46)	HC (*n* = 20)	Instability: MSSD	BSD group reported greater instability in ratings of happiness and sadness in comparison to HC group but did not differ in levels of instability in ratings of feeling energetic or relaxed.
2. Bowen et al. (2017)	Depression (*n* = 74)	HC (*n* = 59)	Instability: MSSD	Depressed group reported more severe instability for negative affect, but no differences were found in levels of instability for positive affect. Negative affect instability and positive affect instability were significantly correlated in depressed group compared to a weak correlation in the non-depressed group.
3. Cowdry et al. (1991)	UD (*n* = 10)	BPD (*n* = 16) PMS (*n* = 15) HC (*n* = 24)	Variability: Within-person SD, day-to-day Within-day Inertia: autocorrelation	UD group reported significantly lower variability in affect in comparison to BPD and PMS groups on all variables and in comparison to HC group on some variables (total and within-day variability). Total variability in affect did not differ between BPD and HC groups. BPD group reported significantly higher within-day variability compared to the other groups.
4. Crowe et al. (2019)	UD (*n* = 31)	HC (*n* = 33)	Variability: Within-person SD Instability: MSSD	Increased variability and instability of negative affect was found in UD group. Increased variability and instability of positive affect was also found in the UD group but to a lesser extent.
5. Ebner-Priemer et al. (2015)	BPD 3 datasets: Study 1: *n* = 50 Study 2: *n* = 42 Study 3: *n* = 43	HC 3 datasets: Study 1: *n* = 50 Study 2: *n* = 24 Study 3: *n* = 28	Variability: Within-person variance Inertia: attractor strength – autoregressive slope	BPD group exhibited higher levels of variability in both valence and distress in comparison to HC group. BPD group exhibited a more negative affective homebase with greater levels of distress in comparison to HC group. BPD group did not exhibit significant differences in attractor strength for each dimension; exhibited lower attractor strength for valence and distress, although the findings for distress were smaller in magnitude and less reliable. All estimations suggested a lower attractor strength for BPD.

6. Ebner-Priemer et al. (2007)	BPD (*n* = 50)	HC (*n* = 50)	Instability: MSSD	BPD group exhibited heightened affect instability for both valence and distress dimensions in comparison to HC group. This heightened affect instability was characterised by sudden large decreases in positive mood states.
7. Gershon et al. (2012)	BSD-I (*n* = 32)	HC (*n* = 36)	Instability: MSSD	BSD group exhibited significantly higher and more variable levels of negative affect. There were no significant group differences in mean level or level of variability of positive affect.
8. Golier et al. (2001)	PTSD (*n* = 15)	UD (*n* = 17) HC (*n* = 17)	Variability: Within-person SD	UD group exhibited significantly lower mood variability in comparison to HC group
9. Hall et al. (1991)	Depressive disorder (*n* = 9)	HC (*n* = 9)	Variability: Within-person SD	Depressed group exhibited significantly more mood variability.
10. Heininga et al. (2019)	UD (*n* = 47)	HC (*n* = 44)	Variability: Within-person variance Instability: RMSSD Inertia: autocorrelation	UD group reported lower levels of positive affect but did not exhibit greater levels of variability, instability, or inertia of positive affect in comparison to HC group. UD group did not exhibit increased inertia of negative affect in comparison to HC group.
11. Houben et al. (2016)	BPD (*n* = 34)	HC (*n* = 28)	Variability: Within-person SD Instability: MSSD	BPD group exhibited significantly more variability and instability of affect in comparison to HC group.

12. Köhling et al. (2016)	UD and BPD (*n* = 20)	UD (*n* = 21)	Instability: SSD	No significant differences in affect instability were observed between the groups even when controlling for depressive symptom severity.
13. Lamers et al. (2018)	BSD-I (*n* = 33)	BSD-II (*n* = 37) UD (*n* = 116) Anxiety disorder (*n* = 36) HC (*n* = 65)	Variability: within-person SD Instability: MSSD Inertia: Autocorrelation	BSD-I group reported the greatest variability in sad affect, but BSD-II and UD group exhibited significantly greater instability of sad mood in comparison to HC controls. All clinical groups exhibited greater variability and instability in anxious mood in comparison to HC group. No group differences were observed in relation to inertia of affect. Variability did not differ between current and remitted UD groups.
14. Li et al. (2019)	BSD (*n* = 10)	HC (*n* = 10)	Variability: Within-person SD	BSD group reported significantly elevated variability within mood.
15. Lovejoy and Steuerwald (1995)	Cyclothymia (*n* = 12)	Intermittent depression (*n* = 16) HC (*n* = 19)	Variability: Within-person SD	Clinical groups were differentiated from HC group on levels of variability of trait and daily ratings of negative affect. Bipolar group exhibited high between-day variability for both positive and negative affect whereas unipolar depression group exhibited high variability only for negative affect. Bipolar group reported significantly higher levels of trait and daily ratings of positive affect in comparison to HC group.
16. McGowan et al. (2021)	BSD (*n* = 38)	BPD (*n* = 25) HC (*n* = 43)	Instability: RMSSD	BPD group exhibited significantly higher levels of instability of anxiety, sadness, elation, energy, anger, and irritability in comparison to HC group. BSD group exhibited significantly higher levels of instability of anxiety, sadness, anger, and irritability in comparison to HC group. BPD group exhibited significantly higher levels of instability of anxiety, sadness, anger, energy, and irritability in comparison to BSD group.

17. Mneimne et al. (2018)	BPD (*n* = 38)	BSD (*n* = 14) UD (*n* = 15) HC (*n* = 62)	Instability: MSSD Inertia: modelled as extent to which an emotion at any given time maintained at next report	Elevated levels of instability in anger and irritability were observed across the clinical groups. High levels of inertia in irritability were also observed across the clinical groups. BPD group additionally exhibited high levels of instability and inertia of guilt and shame.
18. Moukhtarian et al. (2021)	BPD (*n* = 19)	ADHD (*n* = 28) ADHD and BPD (*n* = 22) HC (*n* = 29)	Instability: SSD	Significantly higher levels of instability of negative affect were observed in BPD group in comparison to HC. No significant differences were observed in levels of instability of positive affect between clinical and HC groups.
19. Napolitano et al. (2021)	BPD (*n* = 56)	Community controls (*n* = 60)	Instability: SSD	BPD group exhibited increased levels of instability of negative affect.
20. Ortiz et al. (2015)	BSD (*n* = 30)	HC (*n* = 30)	Variability: Entropy calculations	No statistical differences were found between BSD and HC groups in autocorrelation of mood. Entropy levels were higher in the HC group in comparison to BSD group, but this difference was not statistically significant.
21. Peeters et al. (2006)	UD (*n* = 47)	HC (*n* = 39)	Variability: Within-person SD	UD group exhibited lower overall levels and decreased interindividual variation in positive affect and higher overall levels and greater interindividual and moment-to-moment variance in negative affect. Moment-to-moment variability in mood states was more dysregulated in clinically severe participants.

22. Pincus et al. (2008)	PMDD (*n* = 15)	Recurrent depressive disorder (*n* = 9) HC (*n* = 8)	Variability: Within-person SD Day-to-day variance Within-day variance	Highly significant differences were observed in variability of affect across the different groups. RBD group could only be differentiated from HC group on the basis of variability of affect, although there were subtler differences observed on spikiness of affect. RBD group's levels of variability of affect lay in between PMDD and HC.
23. Russell et al. (2007)	BPD (*n* = 30)	HC (*n* = 44)	Variability: Flux (within-person SD)	BPD group reported increased levels of intraindividual variability in affect valence. No significant differences were observed in levels of flux in negatively valenced affect when controlling for mean level and quadratic level of affect. Both groups reported similar mean levels of positive affect, but BPD group exhibited elevated intraindividual variability in BPD.
24. Santangelo et al. (2020)	BPD (*n* = 60)	Remitted BPD (*n* = 35) HC (*n* = 60)	Instability: SSD, PAC, APPC	No significant differences were observed in affect instability between the clinical groups. Both BPD and remitted BPD groups reported higher levels of affect instability in comparison to HC group.
25. Santangelo et al. (2018)	BPD (*n* = 130)	HC (*n* = 130)	Instability: SSD	BPD group reported significantly higher levels of affect instability in valence and tense arousal in comparison to HC group. Controlling for mean level of affect did alter these group differences. Controlling for comorbidity and severity of BPD symptoms did not change the findings.
26. Santangelo et al. (2017)	BPD (*n* = 60)	HC (*n* = 60)	Instability: SSD, PAC, APPC	BPD group reported higher levels of affect instability in comparison to HC group. Estimated means and odds of acute changes in affect were lower in BPD group in comparison to HC group. Affect instability was related to level of general psychopathology in BPD group.

27. Santangelo et al. (2014)	BPD (*n* = 43)	PTSD (*n* = 28) Bulimia nervosa (*n* = 20) HC (*n* = 28)	Instability: MSSD, PAC	BPD group reported higher instability of affect across all statistical indices. No significant differences were observed in affect instability across the clinical groups. Controlling for mean levels of valence and distress did not change the findings.
28. Scheiderer et al. (2016)	BPD (*n* = 78) (33 also met criteria for PTSD)	UD/Dysthymia (*n* = 50)	Instability: MSSD, detrended MSSD	BPD group exhibited elevated levels of affect instability in comparison to UD/DYS group for each affect category.
29. Scott et al. (2020)	Spectrum of diagnoses (*n* = 156) Internalising: UD, dysthymia, panic disorder, social phobia, specific phobia, PTSD, GAD, BPD. Externalising: BPD, ASPD, alcohol use, drug use		Variability: Innovation variances Inertia: Autoregressive coefficients	Internalising disorders were associated with higher levels of variability of negative affect, and lower levels of variability of positive affect but were not associated with inertia of negative affect. Externalising disorders were associated with lower levels of inertia of positive affect and higher levels of variability of positive affect but were not associated with higher levels of variability of negative affect or affect polarisation.
30. Servaas et al. (2017)	UD (*n* = 62)	HC (*n* = 41)	Instability: MAASD	UD group exhibited heightened levels of instability in feeling agitated, down, irritated, restless and worry. No significant differences of were observed in measures of instability for other variables. UD group exhibited elevated levels of variability in feeling enthusiastic, cheerful, relaxed, satisfied and empowered.
31. Snir et al. (2017)	Avoidant personality disorder (*n* = 43)	BPD (*n* = 57) HC (*n* = 53)	Instability: MSSD, PAC	BPD group exhibited higher levels of affect instability in comparison to HC group. 82.5% of individuals in BPD group were above the threshold for the borderline affective instability criterion.

32. Sperry et al. (2020)	BSD (*n* = 15)	Subclinical BSD (*n* = 22) Hypomania (*n* = 22) UD (*n* = 28) Depressive episode (*n* = 42)	Variability: Within-person SD Instability: MSSD, PAC Inertia: autocorrelation	BSD psychopathology was associated with heightened variability and instability in negative and positive affect. This association was strongest in individuals with broad BSD diagnoses and hypomanic personality. Variability of negative affect was the only index that differentiated those with a DSM diagnosis of BSD and predicted development of new BSD diagnoses. Abnormal affect dynamics were not associated with UD and depressive episode groups; however, variability and instability of negative affect were associated with depressive symptoms. Altered inertia of affect was not associated with psychopathology across all groups.
33. Stein (1995)	BPD (*n* = 15)	Anorexia nervosa (*n* = 4) HC (*n* = 10)	Variability: Within-person SD	BPD group reported heightened levels of unpleasant and activated unpleasant affects, and greater variability in unpleasant affect in comparison to HC group. No significant differences were found for instability of pleasant, activated pleasant, and unactivated pleasant affective states, despite these scores being comparable to those found for the three unpleasant affect states. HC group exhibited considerable fluctuations in pleasant affects which was in marked contrast to smaller levels of variability noted for unpleasant affects in HC group. No differences were observed in persistence of unpleasant affect states over time between BPD and HC or AN.
34. Stein (1996)	BPD (*n* = 15)	Anorexia nervosa (*n* = 4) HC (*n* = 10)	Variability: Within-person SD	Significantly higher levels of instability of negative affect were observed in clinical sample.
35. Thompson et al. (2012)	UD (*n* = 53)	HC (*n* = 53)	Variability: Within-person SD Instability: MSSD Inertia: autocorrelation	UD group exhibited heightened instability of negative affect but not positive affect in comparison to HC group. Depression status was associated with instability of negative affect even after controlling for average levels of negative affect. Neither group was characterised by heightened levels of inertia and there were no significant differences between groups in levels of inertia.

36. Trull et al. (2008)	BPD (*n* = 34)	UD/Dysthymia (*n* = 26)	Variability: Within-person SD Instability: ASSD, AAC	BPD group was characterised by heightened variability in positive affect scores but not by instability or probability of acute changes in positive affect. BPD group was further characterised by increased variability in negative affect, heightened instability for hostility, fear and sadness, and were more likely to report extreme changes across successive scores for hostility.
37. Tsanas et al. (2016)	BSD (*n* = 53)	BPD (*n* = 33) HC (*n* = 53)	Variability: Within-person SD Instability: RMSSD, Teager-Kaiser Energy Operator, entropy	BPD group exhibited heightened variability and instability in negative emotions, increased instability in positive affect, and greater variability in irritability. The biggest effect was observed for variability in irritability. Differences in levels of affect variability tended to be more marked with TKEO and RMSSD. Both clinical groups showed greater variability and instability of negative and positive affect, and irritability in comparison to HC group.
38. van de Leemput et al. (2014)	Depressed (*n* = 93)	HC (*n* = 535)	Variability: Within-person SD Inertia: autocorrelation	Inertia and affect variability were elevated in individuals with upcoming transitions to depressive episode. The association between these indices of altered affect dynamics and impending worsening of depressive symptoms was strongest for negative affect. The opposite was found for positive affect – elevated levels of inertia and variability in positive affect were found to predict upcoming improvements in depressive symptoms in individuals with current UD.

Note.

[a] Parameters of EMA/ESM protocol are listed in Table 2.

ADHD: attention deficit hyperactivity disorder; ASPD: antisocial personality disorder; BSD: bipolar spectrum disorder; BSD-I: bipolar disorder type I; BSD-II: bipolar disorder type II; BPD: borderline personality disorder; GAD: generalized anxiety disorder; HC: healthy controls; UD: unipolar depression; PMDD: premenstrual dysphoric disorder; PMS: premenstrual syndrome; PTSD: post-traumatic stress disorder

AAC: adjusted acute change; APPC: aggregated point-by-point change; ASSD: squared successive difference; MAASD: mean-adjusted absolute successive difference; MSSD: mean squared successive difference; PAC: probability of acute change; RMSSD: root mean squared successive difference; SD: standard deviation; SSD: squared successive difference

3.3. Participants

The sample size in the studies varied between 18 and 628 (mean = 197.95). The mean age of the study samples was calculated as ranging from 18 to 51.8 years for all except two studies, who did not report mean age but did report ranges of 18 – 21 years, with 79% of sample reported to be 18/19 years[15], and 18 – 45 years[3]. The mean age across all studies was 33.42 (*8.16*). The percentage of female participants in the study samples was calculated as ranging from 62.6% to 100% and a mean of 81.7% (*14.82%*). Twelve studies consisted of all-female samples[3, 5, 6, 12, 18, 22-27, 29] and one study consisted of an all-male sample[8].

All studies included participants who currently met diagnostic criteria for bipolar spectrum disorder (BSD), unipolar depression (UD) or borderline personality disorder (BPD), which were confirmed using standardised diagnostic criteria. Nine studies' primary clinical group was BSD[1, 7, 13-16, 20, 32, 37]. Nine studies' primary clinical group was UD[1, 3-4, 9-10, 21, 30, 35, 38] and sixteen studies' primary clinical group was BPD[5-6, 11-12, 17-19, 23-28, 33-34, 37]. Four studies' primary clinical group was not BSD, UD or BPD, although one or all of these groups were included as clinical controls. Primary clinical groups in these studies included a spectrum of diagnoses including UD, dysthymic disorder, panic disorder, social phobia, specific phobia, post-traumatic stress disorder (PTSD), generalised anxiety disorder, BPD, antisocial personality disorder, alcohol use and drug use[29], avoidant personality disorder[31], premenstrual dysphoric disorder[22], and PTSD[8]. Only five studies did not include a healthy control group[12, 28-29, 32, 36]. Twenty-seven studies included a clinical control group including BPD[3, 16, 31, 37], ADHD and ADHD with comorbid BPD[18], remitted BPD[24], subclinical BSD, hypomania and depressive episode[32], depressive disorder[8, 12-13, 15, 17, 22, 28, 32, 36], anxiety[13], BSD[13, 17], bulimia nervosa[27], PTSD[27], anorexia nervosa[33-34] and premenstrual syndrome[3].

3.4.EMA/ESM Methodology

3.4.1 Data Collection Period, Sampling Rate, Modality, and Design

Details of the EMA/ESM methodology used across the studies are shown in Table 2. There was considerable variation in the EMA/ESM parameters selected across the studies. The average data collection period was calculated as 26.89 days (*SD* = 62.05) and ranged from 1 to 360 days across the studies. Eight studies used smartphones or iPods[1, 10, 14, 16, 18, 25, 29, 37], fourteen studies used a palm pilot or handheld computer[5-6, 11, 13, 17, 19, 24- 28, 30-31 35-36], two used Personal Digital Assistant device (PDA)[12, 32], and fourteen used paper and pen to collect data[2-4, 7-9, 15, 20-23, 33-34, 38]. The average sampling rate was calculated as 9.71 (*SD* = 12.32) and ranged from 1 to 58.5. The majority (94%) of studies used a signal-contingent design in which the study device emitted a beep that prompted participants to complete the measure. Approximately half of these studies, used a quasi-random design in which the signal was emitted at a random point within a fixed time interval [5, 10-13, 16, 18-19, 24-25, 29-30, 33-36, 38]. The remainder either used a fixed schedule in which signals were emitted at fixed-timepoints regularly spaced throughout the day[2, 3, 7, 9, 15, 17, 20, 22, 26, 37] or did not report the timing of the emitted signals[4-5, 8, 21, 27-28, 31]. One study employed an event-contingent design in which participants were required to complete the EMA/ESM measure in following a social interaction[23]. Another study employed a similar event-contingent design in addition to a signal-contingent design[19].

3.4.2. Affect Measures

There was significant variation in the individual affect items, rating scales and anchor points employed in EMA/ESM measures (Table 2). Six studies used affect items from the PANAS[7, 15, 19, 28-29, 36], six used a VAS measure[3, 8-9, 14, 20, 22], and the remainder of the studies

employed a custom measure. Twenty-three studies included individual items relating to both positive and negative affect dimensions[1, 4-7, 12, 15-18, 21, 23, 26, 28- 30, 32-38]. Three studies examined negative affect exclusively[19, 22, 31] and one study examined positive affect exclusively[10]. Eleven studies included bipolar measures which placed high and low affect on either end of the rating scale[2-3, 8-9, 11, 13-14, 20, 24-25, 27]. The majority of studies (81.58%) calculated indices of affect dynamics based on affect dimensions of high and low valence and arousal or activation[2-15, 18-25, 30- 35, 38]. Four studies included calculations for additional affect dimensions such as irritability[16, 37] or hostility[28, 36]. Two studies calculated indices based on individual items such as happy or sad[1, 17].

3.4.3. Calculation and Analysis of Affect Dynamic Parameters

The majority of studies focused on measures of affect variability (55.26%)[3-5, 8-11, 13-15, 20-23, 29, 33-38] and instability (68.42%)[1, 2, 4, 6-7, 10-13, 16-19, 24-28, 30-32, 35-37]. Nine studies included a measure of affective inertia in their analyses[3, 5, 10, 13, 17, 29, 32, 35, 38]. A large proportion of studies (55.26%) employed multilevel modelling to analyse the EMA/ESM data, create and compare the parameters across clinical groups[4-5, 10-14, 17-18, 21, 23-29, 31, 35-36, 38]. There was considerable variation in the statistical methods used in the remainder of the studies (Table 2).

Table 2.

Included Studies: Parameters of EMA/ESM Protocol

Study	Data Collection Period (days)	Modality	Sampling rate: (prompts per day)	Recording design	Affect Measure	Affect Items	Rating Scale	Affect Composite	Statistical test to compare groups
1. Bomyea et al. (2021)	14	Smart phone	3	Signal-contingent; quasi random	Custom	Energetic, happy, relaxed, sad, stressed	1 to 7	Individual items	Independent *t*-tests
2. Bowen et al. (2017)	7	Paper and pen	2	Fixed Schedule: morning and evening	Custom	Low mood: sad/blue and depressed High mood: enthusiastic/interested	Not reported	Low and high mood	Independent *t*-tests
3. Cowdry et al. (1991)	14	Paper and pen	2	Fixed Schedule: morning and evening	VAS	VAS Worst I've ever felt Best I've evert felt	0 to 100 Or 1 to 24	Valence	Kruskal-Wallis tests
4. Crowe et al. (2019)	6	Paper and pen	10	Signal-contingent	Custom	Anxious, ashamed, down, enjoying myself, guilty, happy, interested, irritable, relaxed, tense.	1 to 7	Positive and negative affect	Multilevel modelling

5. Ebner-Priemer et al. (2015)	1 – 4	Palmtop computer	Unspecified Dataset 1 and 3: every 15 minutes Dataset 2: Every hour	Signal-contingent	Custom and Multi-dimensional Mood Questionnaire	Angry, anxious, disgust, envy, guilty, happy, interest, pleasant shame, sad, unpleasant. Questionnaire: unwell-well and tense-relaxed.	11-point Likert or 0 to 6	Valence, distress, arousal	Multilevel modelling
6. Ebner-Priemer et al. (2007)	1	Palmtop computer	Unspecified Every 10 – 20 minutes	Signal-contingent; quasi random	Custom	Angry, anxious, disgust, happy, interest, sad, shame, emotion but can't name it, no emotion	11-point Likert Scale	Positive and negative affect	Independent *t*-tests Wilcoxon tests
7. Gershon et al. (2012)	54 ± 8	Paper and pen	1	Fixed Schedule: morning and evening	PANAS	Active, afraid, alert, ashamed, attentive, determined, distressed, excited, enthusiastic, guilty, hostile, inspired, interested, irritable, jittery, nervous, proud, scared, strong, upset	1 to 5	Positive and negative affect	Mann-Whitney U test
8. Golier et al. (2001)	1	Paper and pen	Unspecified Every 60 minutes	Signal-contingent	VAS	Mood: very sad to very happy Anxiety: very anxious to very tense	0 to 100	Mood and anxiety	Independent *t*-tests

9. Hall et al. (1991)	1	Paper and pen	13	Fixed Schedule: consecutive hourly reports	VAS	Worst, sad Best, happy	0 to 100	Valence	Mann-Whitney U test
10. Heininga et al. (2019)	7	Smart phone	10	Signal-contingent; quasi random	Custom	Euphoric, happy, relaxed.	0 to 100	Positive - high, neutral and low arousal	Multilevel modelling
11.Houben et al. (2016)	8	Palmtop computer	10	Signal-contingent; quasi random	Custom	How pleasant and activated/passive	0 to 100	Valence and activation	Multilevel modelling
12. Köhling et al. (2016)	7	PDA	5	Signal-contingent; quasi random	Custom	Angry, anxious, content, empty, guilty, happy, lonely, relaxed, sad, tense.	1 to 7	Positive and negative affect	Multilevel modelling
13. Lamers et al. (2018)	14	Palm pilot	4	Signal-contingent; quasi random	Custom	Very happy to very sad Very calm to very anxious	1 to 7	Valence and arousal (high and low)	Multilevel modelling ANOVA
14. Li et al. (2019)	14	Smart phone	2	Signal-contingent; random	VAS	Most down/depressed to most up/elated	0 to 100	Positive and Negative affect	Multilevel modelling Intraclass coefficients

15. Lovejoy and Steuerwald (1995)	28	Paper and pen	1	Signal-contingent; fixed schedule	PANAS	Active, afraid, alert, ashamed, attentive, determined, distressed, excited, enthusiastic, guilty, hostile, inspired, interested, irritable, jittery, nervous, proud, scared, strong, upset	1 to 5	Positive and Negative affect	ANOVA
16. McGowan et al. (2021)	7	Smart phone	10	Signal-contingent; quasi random	Custom	Angry, anxious, elated, energetic, irritable, sad	0 to 6	Positive, Negative and Irritable Affect	ANOVA Kruskal-Wallis tests
17. Mneimne et al. (2018)	14	Palm Pilot	5	Signal-contingent; fixed schedule	Custom	Angry, ashamed, excited, guilty, happy, irritable.	0 to 6	Individual items	Multilevel modelling
18. Moukhtarian et al. (2021)	5	iPod	8	Signal-contingent; quasi random	Custom	Angry, excited, happy, irritable, sad	0 to 100	Positive and Negative Affect	Multilevel modelling
19. Napolitano et al. (2021)	21	Palmtop computer	6	Signal-contingent; quasi random and event-contingent	PANAS	21 negative affect items – specific items not reported	1 to 5	Negative Affect	Independent *t*-tests

20. Ortiz et al. (2015)	90	Paper and pen	2	Signal-contingent; fixed schedule	VAS	Mood – specific items not reported	1 to 9	Mood and anxiety	ANOVA
21. Peeters et al. (2006)	6	Paper and pen	10	Signal-contingent	Custom	Agitated, anxious, cheerful, easily distracted, energetic, enthusiastic, guilty, happy, irritable, irritated, restless, strong, satisfied, self-assured, talkative, tense	1 to 7	Valence and activation	Multilevel modelling
22. Pincus et al. (2008)	60 – 120	Paper and pen	1	Signal-contingent; fixed schedule	VAS	Sadness, depression, anxiety	0 to 100	Sadness	ANOVA
23. Russell et al. (2007)	20	Paper and pen	10	Event-contingent; social interaction	Custom	Angry/hostile, depressed/sad, enjoyment/fun, frustrated, happy, joyful, pleased, unhappy, worried/anxious	0 to 6	Pleasant and unpleasant	Multilevel modelling
24. Santangelo et al. (2014)	4	Palmtop computer	12	Signal-contingent; quasi random	Custom	Unpleasant – pleasant Restless/under tension – calm/relaxed	0 to 6	Valence and arousal	Multilevel modelling

25. Santangelo et al. (2020)	4	Smart phone/ Palmtop computer	12	Signal-contingent; quasi random	Custom	Agitated– calm, Content– discontent Relaxed – tense Unwell– well	0 to 100 or 0 to 6	Valence and arousal	Multilevel modelling
26. Santangelo et al. (2018)	2	Palmtop computer	Unspecified Every 15 minutes	Signal-contingent; fixed schedule	Custom	Angry, anxious, disgust, envy, guilt, happy, interest, sad, shame, emotion but can't name it, no emotion	11-point Likert Scale	Intensity and distress	Multilevel modelling
27. Santangelo et al. (2017)	4	Palmtop computer	12	Signal-contingent	Custom	Agitated– calm, Content– discontent Relaxed – tense Unwell– well	0 to 6	Valence and arousal	Multilevel modelling
28. Scheiderer et al. (2016)	28	Palmtop computer	6	Signal-contingent	PANAS	Active, afraid, alert, ashamed, attentive, determined, distressed, excited, enthusiastic, guilty, hostile, inspired, interested, irritable, jittery, nervous, proud, scared, strong, upset	1 to 5	Positive, negative, hostility, fear, and sadness affect	Multilevel modelling
29. Scott et al. (2020)	21	Smart phone	6	Signal-contingent; quasi random	PANAS	Ashamed, cheerful, delighted, excited, guilty, happy, hostile, irritable, joyful, lonely, proud, sad, scared	1 to 5	Positive and Negative Affect	Multilevel cross-lagged modelling

30. Servaas et al. (2017)	6	Palmtop computer	10	Signal-contingent; quasi random	Custom	Agitated, anxious, cheerful, down, enthusiastic, guilty, irritated, lonely, relaxed, restless, satisfied	0 to 7	Positive and Negative Affect	Mann-Whitney U-test
31. Snir et al. (2017)	21	Palmtop computer	5	Signal-contingent	Custom	Afraid, angry, disappointed, irritated, sad, tense	0 to 4	Negative Affect	Multilevel modelling
32. Sperry et al. (2020)	7	PDA	8	Signal-contingent	Custom	Angry, energetic, enthusiastic, irritable, sad, worried	Not reported	Positive and negative affect	Binary logistic regression
33. Stein (1995)	10	Paper and pen	5	Signal-contingent; quasi random	Custom	48 adjectives - not reported	1 to 5	Valence and arousal (high and low)	ANOVA
34. Stein (1996)	10	Paper and pen	5	Signal-contingent; quasi random	Custom	48 adjectives - not reported	1 to 5	Positive and negative affect	Independent *t*-tests
35. Thompson et al. (2012)	7 – 8	Palmtop computer	8	Signal-contingent; quasi random	Custom	Active, alert, angry, anxious, ashamed, disgusted, frustrated, excited, guilty, happy, sad	1 to 4	Positive and negative affect	Multilevel modelling

36. Trull et al. (2008)	28	Palmtop computer	6	Signal-contingent; quasi random	PANAS and PANAS-X	Specific items not reported	0 to 5	Positive, negative, hostility, sadness, fear	Multilevel modelling
37. Tsanas et al. (2016)	120 – 360	Smart phone	1	Signal-contingent; fixed schedule	Custom	Angry, anxious, elated, energetic, irritable, sad	0 to 7	Positive, negative, irritable affect	Wilcoxon Rank Sum-test
38. van de Leemput et al. (2014)	5 – 6	Paper and pen	10	Signal-contingent; quasi random	Custom	Anxious, cheerful, content, sad	0 to 7	Valence and arousal	Multilevel modelling

Note.
ANOVA: analysis of variance; PANAS: positive and negative affect schedule; PDA: personal digital assistant; VAS: visual analogue scale.

3.5. Patterns of Short-term Affect Dynamics Across Mood Disorders

Due to the variation in EMA/ESM protocols, particularly in terms of data collection period and sampling rate (Table 2), findings across the studies are grouped together in terms of length of data collection period: short: one to four days; medium: five to fourteen days; and long: anything above fourteen days. We have chosen to discuss the findings in this way as the different timeframes may capture different aspects of the emotion processes and dynamics that were being investigated and thus may have implications for the findings discussed below.

3.5.1. Bipolar Spectrum Disorder Compared to Healthy Controls

Nine studies compared affect dynamics in participants with BSD to healthy controls[1, 7, 13-17, 20, 37]. No studies involving participants with BSD used a short data collection period. Five studies used a medium data collection period[1, 13-14, 16-17]. In these studies, in comparison to healthy controls, BSD psychopathology was associated with heightened variability in negative affect such as sad or anxious moods[13-14], and positive affect[14]. BSD psychopathology was similarly associated with elevated levels of instability in negative affect including angry, anxious, irritable, and sad moods[1, 13, 16, 17], and positive affect such as happy moods[1]. No altered levels of variability and instability were reported for energetic or relaxed moods[1, 16]. Inconsistencies were present when examining findings related to inertia of affect in these studies. Some studies did not report any findings for altered inertia[13] whereas others reported higher levels of inertia in irritability in comparison to healthy controls[17]. Interestingly, one study found that although BSD psychopathology was associated with increased variability and instability in negative and positive affect overall, differences emerged when looking at the

different subtypes such that individuals with a BSD Type-I diagnosis reported the greatest variability in sad affect, whereas those with a BSD Type-II diagnoses exhibited heightened instability in sad affect[13].

Four studies used a long data collection period[7, 15, 20, 37]. There were inconsistent findings across these studies. Some studies reported increased variability in negative affect in individuals with BSD[7, 15, 37], whereas others did not observe increased levels of affective variability[20]. Similar inconsistencies were observed for variability of positive affect; some studies reported increased levels in individuals with BSD in comparison to healthy controls[15, 37], whereas one study did not find any significant differences between individuals with BSD and healthy controls[7]. Only one study examined levels of affective instability and found heightened levels of instability in negative and positive affect, and irritability in individuals with BSD in comparison to healthy controls[37]. No studies examined alterations in inertia in affect.

3.5.2. Unipolar Depression Compared to Healthy Controls

Fourteen studies compared affect dynamics in participants with UD to healthy controls[2-4, 8-10, 13, 15, 17, 21-22, 30, 38]. Two studies used a short data collection period[8-9]. There were conflicting findings between these two studies; one study found that in comparison to healthy controls, depressive psychopathology was associated with significantly lower mood variability[8], whereas another found that the depressed group exhibited significantly more mood variability than healthy controls[9].

Eight studies used a medium data collection period[2-4, 10, 13, 21, 30, 38]. There were similar inconsistencies in these findings. Some studies observed increased levels of variability in negative affect[4, 21], positive affect[4, 30] and anxious mood[13] in people with UD in comparison

to healthy controls. Similarly, one study observed that heightened variability in negative affect was associated with upcoming worsening of depressive symptoms[38]. However, some studies observed decreased levels of affect variability[3], decreased levels of variability in positive affect[21], and still others reported no significant differences in levels of variability of positive affect[10]. Further, one study observed that elevated variability of positive affect was found to predict upcoming improvements in depressive symptoms in individuals with a current depressive disorder[38]. Similarly, some studies reported increased levels of instability of negative affect[2, 4, 13], positive affect[4] and individual affect items: anxious mood[13], and agitated, down, irritated, restless and worry[30]. However, other studies reported no differences observed in levels of instability of positive affect between depressed and health individuals[2, 10, 30]. However, one study observed that instability of negative and positive affect were highly correlated in individuals with depression, which was not seen in healthy controls[2]. These findings suggest that fluctuations of negative and positive affect are more closely related in individuals with depression[2]. In the two studies that examined levels of inertia, no group differences were observed in relation to inertia of either negative or positive affect[10, 30].

Four studies used a long data collection period[15, 17, 22, 29]. In comparison to healthy controls, depressive psychopathology was consistently associated with heightened variability in negative affect[15, 22], however, no significant differences in variability of positive affect were observed between depressed individuals and healthy controls[15]. In contrast, heightened instability of negative affect was consistently associated with depressive psychopathology[17, 22, 35], whereas no differences were observed in levels of instability of positive affect[35]. There were further inconsistencies in comparison of inertia of affect. One study observed higher

levels of inertia in irritability in individuals with UD[17], whereas another other study did not observe significant differences between groups in levels of inertia[35].

3.5.3. Borderline Personality Disorder Compared to Healthy Controls

Seventeen studies compared affect dynamics in participants with borderline personality disorder (BPD) to healthy controls[3, 5-6, 11, 16-19, 23-27, 31, 33-34, 37]. Six studies used a short data collection period[5-6, 24- 27]. Across these studies, borderline psychopathology was consistently associated with higher levels of affect variability in both valence and distress[5] and was further associated with heightened levels of affect instability in valence[6, 24-27], distress[6], and tense arousal[25]. Controlling for mean levels of affect valence and distress did not alter these group differences[25-26]. Similarly elevated levels of affect instability were also found in individuals with remitted BPD in comparison to healthy controls[24].

Seven studies used a medium data collection period[3, 11, 16-18, 33-34]. Similar to the above findings, borderline psychopathology was consistently associated with higher levels of variability and instability of negative affect in comparison to healthy controls[3, 11, 16-18, 33-34]. Individuals with BPD exhibited significantly elevated levels of instability of negative affect[18] and specific negative affect items such as anger and irritability[16-17], anxiety and sadness[16], and guilt and shame[17] in comparison to healthy controls. However, there were inconsistencies relating to differences in variability and instability of positive affect. One study reported significantly higher levels of instability of positive affect items[16], whereas two other studies did not find significant differences between BPD and healthy control groups in levels of variability of positive affect[33] or instability of positive affect[18]. Only one study compared levels of inertia, and observed higher levels of inertia of irritability, guilt and shame in individuals with BPD in comparison to healthy controls[17].

Four studies used a long data collection period[19, 23, 31, 37]. In agreement with the above findings, in comparison to healthy controls, borderline psychopathology was consistently associated with higher levels of variability and instability of affect[19, 23, 31, 37]. More specifically, borderline psychopathology was associated with increased levels of instability of negative affect[19, 37], increased levels of variability and instability of positive affect[23, 37] and increased levels of variability and instability of irritability[37]. However, one study noted that the observed differences between the BPD and healthy control groups in levels of variability of negative affect were no longer significant when controlling for mean level and quadratic level of affect[23].

3.5.4. Comparisons of Patterns of Affect Dynamics Across Different Forms of Psychopathology

Some studies included clinical control groups of psychiatric disorders that were not the focus of this review, including anxiety disorders[13], attention deficit hyperactivity disorder[18], post-traumatic stress disorder[8,27, 28], premenstrual syndrome[3], bulimia nervosa[27], anorexia nervosa[33, 34], avoidant personality disorder[31] and premenstrual dysphoric disorder[22]. As these disorders were not the focus of this review, we will not review these findings here. However, significant findings and observations are noted within Appendix B.

Eleven studies compared affective dynamics across bipolar, depressive, and borderline personality disorders[3, 12-13, 15-17, 28-29, 32, 36-37]. No studies used a short data collection period. Eight studies used a medium data collection period. Only one study included comparisons across all three disorders and observed high levels of instability of anger and irritability, and high levels of inertia in irritability across all three clinical groups[17]. However, the BPD group additionally exhibited heightened levels of instability and inertia of guilt and shame in comparison to bipolar and depressive groups[17]. Inconsistent findings are evident

when examining studies that compared depressive and borderline groups; some found evidence for an association between elevated levels of affect variability[3] and instability of negative and positive affect with borderline psychopathology, and an association between decreased levels of affect variability and depressive psychopathology[28]. In contrast, one study did not find any significant differences in affect instability, even when controlling for depressive symptom severity[12]. Similar inconsistencies are present in studies comparing bipolar and depressive psychopathology. One study observed that individuals with bipolar disorder exhibited elevated variability for both positive and negative affect, whereas individuals with UD exhibited elevated variability only for negative affect[15]. Another study similarly observed that bipolar psychopathology was associated with elevated variability and instability in negative and positive affect[32]. However, this study did not observe an association between altered affective dynamics and depressive psychopathology[32]. Nevertheless, this study did find that variability and instability of negative affect were associated with depressive symptoms[32]. Another study did not report significant differences between bipolar and depressive groups in overall affect variability, instability, and inertia; all clinical groups showed elevated levels of variability and instability in anxious mood[13]. When examining specific affect items, participants with BSD-I, BSD-II or UD all showed significantly greater instability of sad mood in comparison healthy controls, however, participants with BSD-I reported the greatest variability in sad affect[13]. Only one study compared affect dynamics between bipolar disorder and BPD groups and found that participants with BPD reported significantly greater levels of instability of anxiety, sadness, anger, energy, and irritability in comparison to participants with bipolar disorder[16].

Three studies used a long data collection period. Two studies observed that all clinical groups exhibited high levels of affect variability and instability[36-37], and in some cases, these

were significantly different from healthy controls[37]. However, there were subtle differences when comparing the groups across different indices of affective dynamics and dimensions of affect. Both individuals with BPD and individuals with UD reported relatively high mean levels of negative affect[36]. However, individuals with BPD were characterised by significantly higher levels of variability for positive and negative affect, heightened levels of instability for feelings of hostility, fear, and sadness, and were more likely to report extreme changes across successive timepoints for feelings of hostility in comparison to individuals with UD[36-37]. Similarly, although both individuals with BPD and individuals with bipolar disorder exhibited increased levels of variability and instability of positive and negative affect in comparison to healthy controls, individuals with BPD exhibited higher levels of variability and instability in negative affect, instability of positive affect, and variability of irritability in comparison to individuals with bipolar disorder[37]. Therefore, the degree of affect variability and instability was able to differentiate these clinical groups. Finally, internalising psychopathology was shown to be associated with higher levels of variability of negative affect and lower levels of variability of positive affect but was not associated with inertia of negative affect[29]. In contrast, externalising psychopathology has been shown to be associated with disturbed dynamics in positive affect, specifically elevated levels of variability and lower levels of inertia. Externalising psychopathology was not associated with altered affect dynamics for negative affect[29].

4. Discussion

4.1. Summary of Main Results

The current study systematically reviewed studies using EMA/ESM methodology to examine affect dynamics across mood disorders, with a view to understanding whether there are distinct patterns of altered affect dynamics that are characteristic of different forms of psychopathology. Such findings may facilitate differential diagnosis of different disorders, and potentially identify markers that could serve as indicators of treatment efficacy and act as targets for therapeutic interventions themselves. Having synthesised results narratively across different forms of psychopathology, overall findings are generally consistent with the association between affective variability and instability with decreased psychological wellbeing (Houben et al., 2015). Findings further demonstrate that the clinical relevance of affective variability and instability extends to a wider range of psychopathology, rather than the few in which it is an established trait or diagnostic criterion e.g., BPD (Ebner-Priemer et al., 2009).

4.2. Patterns of Affect Dynamics in Bipolar Spectrum Disorder (BSD)

The current review found that BSD psychopathology was associated with more variable and unstable emotions. This fits with the clinical manifestation of BSD, which indicates that it is characterised by periods of extreme disruption to mood with periods of severe depression, hypo/mania and inter-episode period in which individuals can still display mood swings (American Psychiatric Association, 2013). BSD psychopathology was associated with heightened variability and instability in both positive and negative affect. However, there was two studies in which no differences in levels of either variability or instability of affect

(Ortiz et al., 2015) and positive affect (Gershon et al., 2012) were found between individuals with BSD and healthy controls. Interestingly, both of these studies employed a time-contingent design in which data was collected twice a day. It may be that this sampling frequency was too low to track the rapid changes in mood that are characteristic of BSD (Ebner-Priemer et al., 2009). Furthermore, both of these studies employed a paper-and-pen design which is commonly associated with backfilling, which refers to the process of participants completing all entries at once, rather than at prompted times (Stone et al., 2003). This raises the potential for retrospective biases which may influence the data collected, resulting in a smoothing away of affect variation (Ebner-Priemer et al., 2006; Stone et al., 2003).

Only two studies compared levels of affect inertia between individuals with BSD and healthy controls, and conflicting findings were observed. One study, reported no differences in levels of inertia (Lamers et al., 2018), whereas another observed higher levels of inertia in irritability in individuals with BSD relative to healthy controls (Mneimne et al., 2018). Interestingly, the affect measures employed in these two studies differed considerably. Lamers and colleagues (2018) used a custom measure that capture affect states on bipolar dimensions of valence and arousal. In contrast, Mneimne and colleagues (2018) required participants to rate individual affect items such as angry or excited. It may be that the assessment of positive and negative affect simultaneously within a bipolar dimensional scale precluded the detection of more subtle differences in affect inertia between BSD and healthy controls, for example, in feelings of irritability (Gershon & Eidelman, 2015). However, as only two studies compared levels of inertia between individuals with BSD and healthy controls, further research that assesses levels of inertia of positive and negative affect independently,

and further examines inertia of different affective states is required to further elucidate the pattern of affect inertia in BSD.

Overall, the findings from the current review suggest that individuals with BSD are generally described as dysregulated and characterised by rapid and extreme fluctuations in both positive and negative affect. There may be a number of potential mechanisms underlying these affect dynamics. One possibility is that these fluctuations in affect are the result of the hypersensitivity and hyperreactivity of the physiological systems mediating response to reward and punishment (Urošević et al., 2008). However, an alternative approach is a neuro-computational model in which the mood of individual with BSD psychopathology strongly influences their perception of rewards, resulting in repetitive cycles that escalate mood, cognition and behaviour to the extremes seen in depressive and manic episodes (Mason et al., 2017). Within this model, normal fluctuations in affect, which are significantly dependent on reward prediction errors, become amplified as reward perceptions become progressively discordant from actual outcomes. For example, an individual that receives a positive surprise, such as receiving a promotion at work will typically experience a positive affective state. This then influences how the individual perceives future rewards, viewing them to be better than they actually are, which increases the likelihood of this individual choosing high-reward options and experiencing further positive affective states when these rewards are received. This escalation of positive affective states can culminate in manic symptom presentation. This affect-biased reward perception subsequently leads to recursive cycles that underlie the extreme mood states observed in BSD. As reward-based expectations become overly inflated, the mismatch between inflated expectations and actual outcomes may result in a negatively-valenced surprise outcome, which subsequently contributes to deterioration in mood and the presentation of depressive symptoms (Mason et al., 2017).

Thus, affect-biased reward perception and valuation may underlie the increased incidence of fluctuations in affect observed in individuals with BSD (Mason et al., 2017). Another approach has focused on the difficulties in affect regulation and dysfunctional cognitions that are common in BSD (Johnson et al., 2005; Wright & Lam, 2004). Within this approach, dysfunctional beliefs relating to internal states interact with maladaptive affect regulation strategies and lead to frequent and amplified fluctuations in affect that can maintain or exacerbate symptoms (Alloy, Abramson, et al., 2009; Gershon & Eidelman, 2015; Mansell et al., 2007; Pavlickova et al., 2013).

4.3. Patterns of Affect Dynamics in Unipolar Depression

UD has traditionally been characterised by high levels of negative affect, low levels of positive affect, and high levels of affective inertia resulting in a clinical picture of flat and blunted affect for the majority of the day (Sperry et al., 2020; Watson et al., 1988). However, research has shown that once mean levels of affect are accounted for, affective inertia is no longer associated with affect in UD (Dejonckheere et al., 2019). Moreover, Koval and colleagues (2013), found that depressive symptoms were associated with inertia in a lab setting, while when using an ESM design, they were solely associated with variability. The current review found similar inconsistencies in comparisons of inertia of affect between individuals with UD and healthy controls. The majority (n = 3) of studies that included a measure of inertia did not find an association between depressive psychopathology and affective inertia. In contrast, only one study observed higher levels of inertia in irritability in individuals with UD (Mneimne et al., 2018). This highlights the importance of context and lends support to the suggestion that in daily life, depressive symptoms may not be related to affective inertia.

Affect variability or instability has not been historically associated with depressive disorders (Beck, 1967; Bowlby, 1973; Brown & Harris, 2012; Watson, 2000). This may be due to a reliance on retrospective interviewing methods which may contribute to the smoothing away of variation in affect due the negative biases that can occur in UD (Ebner-Priemer et al., 2006). Additionally, brief periods of positive affect may be ignored or dismissed due to the traditionally held view that negative and positive affect are mutually exclusive or negatively correlated (Bowen et al., 2017; Zautra et al., 1997). However, research has shown that negative and positive affect are independent of each other (Russell & Carroll, 1999), and that individuals with depression can experience positive and negative affect concurrently (Larsen et al., 2001). In line with these findings, this review found that UD psychopathology was associated with altered levels of affective variability and instability, although there were some inconsistencies. These inconsistencies mainly related to positive affect; decreased (*n* = 1), heightened (*n* = 2) and no differences (*n* = 5) in levels of variability and instability were found when comparing people with UD to healthy controls. Depressive psychopathology has consistently been associated with hyporesponsivity to reward (Alloy et al., 2016), which supports the finding that individuals with UD show lower levels of variability and instability of positive affect. In contrast, research has observed a mood brightening effect in which UD individuals are more reactive to positive events (Peeters et al., 2003), leading to the prediction that depressed individuals will show greater instability of positive affect; this effect may be counteracted by depressed individuals experiencing fewer positive events. Further, research has shown that depressed individuals' mood brightens more in response to psychological (events that were appraised by participants as positive) rather than behavioural rewards (activities that were appraised by researchers to be rewarding in general such as playing a sport or being with friends) (Heininga et al., 2019). Thus, it may be that discrepancies in

findings are due to individual differences in occurrence of negative and positive events, and the entanglement of events, subjective appraisals of events and affective states (Bakker et al., 2017). However, as a limited number of studies assessed the occurrence of positive and negative events, it is difficult to fully understand the role of events in the affect dynamics.

In contrast, depressive psychopathology was generally associated with elevated levels of variability and instability of negative affect. Similarly, to BSD, there may be a number of potential mechanisms underlying these affect dynamics. These relate to difficulties in affect regulation, dysregulation in biological circadian rhythms and negative biases in cognitive functioning that characterise individuals with depressive psychopathology (Joormann & Vanderlind, 2014). Difficulties in emotion regulation and negative cognitive biases may result in difficulties managing cognitive and affective reactions to activating external and internal events contributing to more labile affect (Crowe et al., 2019; Servaas et al., 2017; Thompson et al., 2012). Further, disruption to biological circadian rhythms such as the Hypothalamic Pituitary Adrenal (HPA) axis could contribute to fluctuations in feelings of fatigue, tiredness, energy, alertness and vigour, which could result in heightened affective variability and instability (Daly et al., 2011).

4.4. Patterns of Affect Dynamics in Borderline Personality Disorder (BPD)

The current review found that BPD psychopathology was associated with heightened levels of affect variability and instability. This is in line with the clinical characterisation of BPD as a disorder that is typified by instability and impulsivity (American Psychiatric Association, 2013). However, although BPD was consistently associated with high levels of variability and instability of negative affect, there were some inconsistencies when looking at levels of positive affect. Although, the majority of studies (*n* = 10) did observe increased levels of

variability and instability of positive affect in comparison to healthy controls, there were two that did not find any significant differences (Moukhtarian et al., 2021; Stein, 1995). Interestingly, Stein (1995) noted that there were considerable fluctuations in positive affect in the healthy control group, which was a marked contrast to the level of variability noted for negative affect in this group. The authors suggested that this difference may have contributed to the lack of significant differences between BPD and healthy control groups. Further, another study examined different indices of variability and demonstrated that although BPD was associated with significantly higher within-day affect variability in comparison to healthy controls, there were no significant differences in total variability in affect (Cowdry et al., 1991). Thus, it may be that taking the total affect variability across a study period may mask important differences between clinical and control groups. This highlights the importance of considering what indices will accurately capture the dynamic processes that researchers are aiming to examine (Trull et al., 2015). Another possible explanation for the inconsistent findings regarding levels of variability and instability of positive affect relates to the argument that individuals with BPD show increased variability in affect as a result of increased reactivity to environmental stimuli (Trull et al., 2008). Interestingly, although Moukhtarian and colleagues (2021) measured the occurrence of negative events, they did not examine the occurrence of positive events. Thus, it is possible that the lack of differences in relation to positive affect dynamics is due to these contextual differences between groups.

Only one study compared levels of inertia between BPD and healthy control groups. This study found that BPD psychopathology was associated with higher levels of inertia in irritability, guilt, and shame. This suggests that feelings of irritability, guilt and shame persist longer from one moment to the next. This is consistent with the clinical picture of BPD as a disorder characterised by difficulties in emotion regulation which contribute to a slow return

to baseline mood (American Psychiatric Association, 2013). Therefore, the dysregulation of affective states in individuals with BPD is typified by rapid mood swings within relatively short periods of time and slow recovery from negative affective states (Sadikaj et al., 2010). This dysregulation may be due to a heightened reactivity to environmental factors, particularly events with an interpersonal element such as social interactions in which individuals with BPD may inaccurately perceive situational cues as indicating risk of rejection or abandonment (Sadikaj et al., 2010). These misperceptions may threaten an individual's sense of security and subsequently trigger negative affect such as guilt, hostility, or shame (Sadikaj et al., 2010). Moreover, individuals with BPD may find themselves in vicious cycles of interpersonal interactions, whereby extreme fluctuations in negative affect may increase the likelihood of experiencing further interpersonal conflicts, which may subsequently lead to further fluctuations in negative affective states (Trull et al., 2008). These negative affective states may persist longer from moment-to-moment due to limited self-soothing capabilities (Stein, 1996). Individuals with BPD typically experience invalidating childhood environments which can hinder the development of self-soothing capabilities required to regulate one's affective states (Kernberg, 1980; Linehan, 1987). Therefore, not only are individuals with BPD are prone to experience more fluctuations in negative affective states, but these states also persist for longer.

4.5. Comparisons of Affect Dynamics Across Different Forms of Psychopathology

Although comparisons between clinical groups and healthy controls are important in establishing differences in affect dynamics that are associated with psychopathology, there are several limitations to these comparisons. Firstly, while results are consistent with the observation that altered affect dynamics, particularly affective variability, and instability, are

associated with lower psychological wellbeing (Houben et al., 2015), comparisons between clinical groups and healthy controls do not indicate the specificity of these altered dynamics to particular forms of psychopathology. Further, clinical groups and healthy controls typically differ in their mean levels of affect which can confound analyses and limit the power of group membership to predict other indices of affect dynamics (Russell et al., 2007). Therefore, comparisons across clinical samples with similar mean levels of affect are needed to clarify whether altered affect dynamics represent transdiagnostic processes or distinct features of specific forms of psychopathology. As noted earlier, this is in line with the recent aims in identifying mechanisms that are transdiagnostic across different forms of psychopathology (Insel et al., 2010).

This review identified altered levels of variability and instability of negative affect and inertia in irritability across BSD, UD and BPD groups. Thus, it appears that altered levels of variability, instability and inertia in negative affect are not specific to any of these disorders. It may be that this pattern of affect dysregulation represents a general vulnerability factor for a larger range of psychopathology then has previously been acknowledged (Lamers et al., 2018). Interestingly, while all groups generally experienced heightened levels of variability and instability of negative affect, with some exceptions (Cowdry et al., 1991), in some studies it was the degree of dysregulation that differentiated BPD from both UD (Scheiderer et al., 2016; Trull et al., 2008) and BSD (McGowan et al., 2021; Tsanas et al., 2016). Hence, it may be that the patterns of dysregulation of negative affect represent a consequence of these disorders and there are simple quantitative differences in the degree to which these disorders impact affect dynamics (Tsanas et al., 2016).

In contrast, it may be that distinct patterns specific to particular forms of psychopathology do exist, but the methodology employed in research has limited the ability

to detect subtle differences in affect dynamics. For example, many studies averaged a set of same-valenced affective states as a proxy for negative and positive affect. However, one study that examined affect dynamics of individual affect items noted that BSD, UD, and BPD groups all showed heightened levels of variability and instability for anger and irritability, however, altered dynamics of guilt and shame were specific to BPD (Mneimne et al., 2018). If these items were analysed together as a proxy for negative affect, these subtle differences would not have been identified. Thus, future research is needed to clarify whether there are subtle differences in patterns of altered affect dynamics across different forms of psychopathology.

4.6. Critical Appraisal of Quality of EMA/ESM Data

There was considerable variation in the EMA/ESM protocol used across the studies to collect data (Table 2). It is vital to consider the impact of this heterogeneity on the findings; for example, differences in study period and sampling interval may result in different temporal aspects of the processes of interest being captured and impeding the comparison of findings across studies (Dunster et al., 2021; Ebner-Priemer & Sawitzki, 2007). Further, research has shown that indices of affect dynamics may differ depending on the type of modality used to collect EMA/ESM data. For example, the use of mobile phones has been associated with higher levels of variability in contrast to paper-and-pen methods (Depp et al., 2012). This may be due to participants backfilling ratings (Stone et al., 2003). Only a few studies that used paper-and-pen methods reported how this was controlled for (Appendix C), and therefore it is unclear how this may have impacted the current findings.

Variation in the analytic techniques used to calculate and compare indices of affect dynamics are especially crucial to consider when conceptualising and assessing concepts such as affective variability and instability. Measures of variability such as within-person standard

deviation have been criticised due to their lack of consideration of temporal dependency of affect ratings (Ebner-Priemer et al., 2009; Trull et al., 2015). Thus, they may reflect an individual's tendency to undergo systematic changes in affect over time, rather than reflecting the variability of affect (Servaas et al., 2017; Trull et al., 2008). It is interesting to note that more recent studies have focused on indices such as the squared successive difference (SSD) to capture fluctuations in affect as they consider temporal dependency (Table 2). Similarly, EMA/ESM methodology result in a substantial amount of data in which multiple factors are evaluated and collected over time and as such they require sophisticated statistical techniques to analyse the data (Baltasar-Tello et al., 2018). Techniques such as multilevel modelling are a relatively recent addition to the field of affect dynamics. Consequently, older studies may have used statistical tools that were inadequate for analysing large amounts of data collected over time (Ortiz et al., 2021). This is important to keep in mind when comparing findings across studies.

Another important consideration is the mean level of affect within groups. It has been shown that many indices of affect dynamics do not contribute to the prediction of psychopathology once mean levels of affect have been controlled for (Dejonckheere et al., 2019). Thus, it is crucial to control for mean level of affect in order to more fully understand whether one group of participants exhibits altered levels of affect dynamics, over and above what might be expected due to individual mean scores (Ebner-Priemer et al., 2008). Few studies reported if they controlled for mean levels of affect therefore it is unclear how this would affect the findings (Appendix C). Missing data is another crucial issue to consider, however, the proportion of missing data and how it was managed was inconsistently reported across the studies (Appendix C). This is particularly important when considering measures of instability such as the SSD (Dunster et al., 2021). As this index and other indices of affective

instability compare successive values, it can be influenced by missing data (Ebner-Priemer et al., 2008).

Finally, the current review did not extract data related to current medication, psychological treatment status, current disorder status, and comorbidity, as this was not consistently reported. Therefore, these factors were not discussed in relation to the findings of the current review. These factors may influence individual differences in affect dynamics and as such it will be important for further research to explore whether there are notable differences in findings when these factors are included in analyses (Lamers et al., 2018). This variation in methodology and quality of evidence has tempered our ability to fully synthesize the aggregate evidence and thus, the conclusions reached are tentative and should not be systematically generalised. The heterogeneity in research published to date and the challenges this creates in comparing findings across studies has prompted the creation of a set of recommendations for all EMA/ESM studies. These include standardized parameters for data collection, the development of an infrastructure to maintain participant privacy, and the systematic evaluation of different platforms for use in EMA/ESM (Chan et al., 2015; Faurholt-Jepsen et al., 2019; Nebeker et al., 2020; Torous et al., 2018).

4.7. Limitations of EMA/ESM Research

The majority of included studies had additional limitations. One such limitation relates to items used to assess positive and negative affect. Several studies employed the Positive and Negative Affect Schedule (PANAS), whereas others assessed affect in terms of valence using Visual Analogue Scales with bipolar dimensions ranging from some derivation of very low to very high mood. The PANAS has been highly criticised due to its overrepresentation of high arousal affect items e.g., anxious or excited, and the exclusion of low arousal items e.g.,

sad or relaxed (Russell & Barrett, 1999). Furthermore, positive and negative affect were generally operationalised as a composite of similarly valenced items. Not only does this prevent the detection of subtle differences across different feeling states, it also ignores the fact that many items will differ in terms of activation, arousal, distress, and associated appraisals and behavioural tendencies (Dejonckheere et al., 2019). This will further limit the detection of subtle differences in patterns of altered affect dynamics across different forms of psychopathology. Similarly, it has been argued that an assessment of positive and negative affect independently would facilitate a more sensitive characterisation of affect than measures that assess positive and negative affect simultaneously e.g., using a bipolar dimensional scale (Gershon & Eidelman, 2015).

Finally, a primary critique of EMA/ESM research is exclusion of contextual information; the majority of studies included in the current review only assessed affective experience and did not ask participants to report emotionally relevant events or daily life stressors during the data collection period (Ebner-Priemer et al., 2007). There will naturally be individual differences in environmental factors encountered in daily life, consequently, individuals will be reacting to different stimuli which introduces an inevitable level of noise into their affective time series (Dejonckheere et al., 2019). Furthermore, if the events that may trigger affective processes are not identified, it will be difficult to ascertain whether differences in affect dynamics reflect differences in the amount and nature of events encountered, or whether they reflect differences in how individuals respond to such events i.e., their affective reactivity (Houben et al., 2015; Russell et al., 2007). Such distinctions are crucial to fully understanding the mechanisms underlying altered levels of affect dynamics across different forms of psychopathology.

4.8 Strengths and Limitations of Current Review

The current review has several strengths and limitations. Strengths of this current systematic review include a focus on multiple forms of psychopathology in which altered affect dynamics have been implicated. Including several psychiatric disorders such as BSD, BPD and UD, facilitated the separation of processes of affect regulation that are involved in psychopathology more generally from those that are unique to specific forms of psychopathology. In addition, we employed a comprehensive search strategy to ensure maximum coverage of studies employing EMA/ESM methodology. This is particularly relevant for the field of EMA/ESM, as the terms are a relatively recent addition to the field of psychological research. Therefore, older studies that employed techniques with a family resemblance to EMA/ESM but did not describe them as such may not have been detected with a less comprehensive literature search. Finally, we comprehensively examined all parameters of EMA/ESM methodology including details about collection period, sampling rate, modality etc. This facilitated a critical appraisal of the evidence-base to date and enabled an exploration of how variation in methodology may have contributed to discrepant findings.

Our findings should be interpreted within the context of several limitations present within the identification of studies, data extraction and synthesis of data. Firstly, although an independent reviewer was involved in the process of study selection, the processes of literature search, data extraction and analysis were conducted solely by the author. Therefore, potential biases may have been introduced, in addition to increasing the likelihood of errors being made. Furthermore, conducting this systematic review as a single researcher who had to extract and synthesise data from a large number of studies, which was time intensive, precluded the inclusion of an assessment of the methodological quality of included studies. Studies of low methodological quality may contribute to the noted inconsistent

findings and as such, an important avenue for future research will be to explore whether there are notable patterns of findings across studies of differing methodological quality. Additionally, the current review only included studies in the English language; hence, there may be other findings related to affect dynamics across BSD, UD and BPD that were not considered. Another limitation relates to the clinical samples used across the studies. The majority of samples were recruited from clinical settings (Appendix C). As a large proportion of individuals affected by psychiatric disorders do not seek treatment, this may have introduced a selection bias into the study and therefore, the findings may not be generalisable to the wider population (Lamers et al., 2018). Similarly, the current review does not include studies of at-risk or non-clinical populations and as such our conclusions may not be applicable to these groups. Future research is needed that focuses on recruiting a wide range of participants encompasses the full spectrum of symptom severity (Bowen et al., 2017; Lamers et al., 2018). Finally, as previously noted, altered affect dynamics form a diagnostic criterion for BPD and as such, researchers are likely to have focused on this disorder when researching abnormal affect dynamics. Therefore, there is likely to be a bias in the literature on affect dynamics based on diagnosis (Marwaha et al., 2014). This bias was borne out in the current review; there were nearly double the number of studies that focused on BPD in comparison to studies that focused on either BSD or UD.

4.9 Conclusions

The studies reviewed here indicate that the clinical significance of altered affect dynamics such as affective instability, extends beyond disorders in which it is understood as a trait or established as a diagnostic criterion such as BPD (Marwaha et al., 2014). Affect dynamics were dysregulated across all forms of psychopathology, including BSD, BPD and UD

in comparison to healthy controls. Specifically, heightened levels of variability and instability of negative affect were found across BSD, BPD and UD groups in comparison to healthy controls. This further supports the argument that affective instability has transdiagnostic potential as an investigational and therapeutic target (Broome et al., 2015). Heightened levels of variability and instability of positive affect were found across BSD and BPD groups in comparison to healthy controls which is in line with clinical characterisations of these disorders; however, there were some conflicting findings in relation to this pattern of affect dynamics in UD groups. Thus, it is still unclear whether dynamics of positive affect are dysregulated in UD psychopathology. Similar inconsistencies were noted for inertia of affect; few studies found evidence of altered levels of inertia across the different forms of psychopathology. In comparisons across clinical groups, it does not appear as though altered levels of dynamics in positive and negative affect are specific to particular forms of psychopathology, although further research is required to clarify this finding as there may be subtle distinctions across different affective states with differing levels of valence, activation and distress. However, it does appear as though the degree of affective variability and instability may differentiate these groups with BPD showing the highest levels, UD the lowest (in comparisons across clinical groups as UD psychopathology was still associated with heightened levels of these affect dynamics in comparison to healthy controls), and BSD lying in the middle of these two. However, although these conclusions have been drawn carefully in light of the heterogeneity in EMA/ESM protocols across the studies, the conclusions reached are tentative and should be further substantiated by future research.

4.10 Implications for Research and Clinical Practice

Due to the variation in EMA/ESM methodology, statistical analysis and findings reported, a meta-analysis was not conducted, and therefore, the findings presented are preliminary. Therefore, future research should seek to aggregate the findings of the current review and analyse them using meta-analysis. This will facilitate the exploration of the impact of variation in parameters in EMA/ESM protocol on patterns of affect dynamics across different forms of psychopathology and will further substantiate the findings of the current review. Additionally, this will also allow for exploration of the association of patterns of affect dynamics with other factors such as age, gender, and diagnostic state. Future research should further seek to explore the relationship between altered patterns of affect dynamics and the context in which they occur and understand the accompanying appraisals of events and meta-cognitions of associated affective processes (Santangelo et al., 2014; Trull et al., 2015). Increasing our understanding of the context in which affective dysregulation occurs, is exacerbated, and subsides will further our understanding of the aetiology and treatment of different forms of psychopathology (Ebner-Priemer et al., 2009; Knowles et al., 2007; Marwaha et al., 2014). This will require EMA/ESM studies that are employ both event-contingent and signal-contingent designs (Trull et al., 2008). Finally, EMA/ESM methodology could be used to explore other clinical factors such as substance abuse, self-harm and suicidal ideation, and their relationship with altered patterns of affect dynamics. Identifying the role of affect and other related factors in suicide attempts may facilitate an understanding of the dynamic patterns of multiple systems in tandem that are involved in suicidal ideation and suicide attempts. This understanding could be used to monitor those at risk for suicide which is one of the most tragic consequences of disorders such as BSD (Stange et al., 2018). However, one of the most fundamental gaps is the heterogeneity of EMA/ESM protocols. As

previously noted, this has resulted in the creation of a set of recommendations for all EMA/ESM studies (Chan et al., 2015; Faurholt-Jepsen et al., 2019; Nebeker et al., 2020; Torous et al., 2018). Future research should endeavour to follow these recommendations to enhance comparability of work.

The current findings offer several implications for clinical practice. Firstly, attention to dysregulated affect dynamics may add an extra dimension to assessment and treatment across psychiatric disorders, particularly those in which current practice does not place a high degree of emphasis on affect dynamics (Bowen et al., 2017). For example, assessing affective instability in an individual with UD may provide useful insights into their use of maladaptive affective regulation strategies and the subsequent experience of additional stressors (Thompson et al., 2012). Attention to affect dynamics can further aid in the differential diagnosis of psychiatric disorders and also provide a more nuanced clinical picture of individual's presentation; for example, asking individuals about the frequency and severity of affective responses to interpersonal interactions, such as guilt and shame may aid in the differential diagnosis of BPD (Mneimne et al., 2018). Assessment and treatment of dysregulated affect dynamics may further increase efficacy of current treatments. Further, dysregulated affect dynamics can act as both a target for interventions and an indicator of treatment efficacy (Broome et al., 2015). For example, the heightened experience of dysregulated feelings of guilt and shame in BPD may provide a target for therapeutic interventions that specifically target these affective states. For example, compassion-focused therapy has previously been used to target the experience of shame in individuals with PTSD (Au et al., 2017). EMA/ESM methodology could also be employed as a self-monitoring tool to increase awareness of affective states, which may aid earlier detection of emerging symptoms and potential difficulties in functioning (Gershon & Eidelman, 2015). Self-

monitoring tools such as mood charts are frequently used in the clinical management of psychiatric disorders and are frequently used across a range of evidence-based psychotherapeutic interventions (Depp et al., 2012; Gershon & Eidelman, 2015; Miklowitz, 2006). Similarly, EMA/ESM methodology could be employed in long-term monitoring of affect dynamics to review treatment progress with patients and predict or partly explain worse long-term clinical outcomes (Gershon & Eidelman, 2015). Long-term monitoring of affect dynamics using EMA/ESM may also facilitate the identification of affect dynamic signatures in individuals that predict imminent events e.g., a transition to a manic episode in BSD or a potential relapse in UD (Broome et al., 2015; Faurholt-Jepsen et al., 2019; Stange et al., 2018). Identification of such signatures offers the opportunity for early intervention, allowing an individual to implement appropriate cognitive or behavioural strategies take additional medication to prevent further deterioration in functioning or potential relapse (Broome et al., 2015; Faurholt-Jepsen et al., 2019).

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Part 2: Empirical Paper

Examining the relationship between neural correlates of reward processing and bipolar mood symptom presentation

Abstract

Aims. The reward hypersensitivity model of bipolar spectrum disorder (BSD) argues that hypersensitivity to reward-related cues is a key contributing factor to its development and onset. The current study sought to examine the relationship between neural correlates of reward processing in a nonclinical sample of adolescents at age 14 with subthreshold mood symptoms at age 14 and 22.

Methods. A subset of adolescents from the community-based IMAGEN study completed baseline clinical and functional Magnetic Resonance Imaging assessments at 14 years (*n* = 1803) and 22 years (*n* = 1104). Neural correlates of reward processing were assessed using the Monetary Incentive Delay task. Hierarchical multiple regression analysis was used to analyse how ventral striatum activation during anticipation of rewards at 14 years was related to self-reported mood symptoms (depressive and (hypo)manic) at 14 and 22 years, whilst controlling for demographic and clinical variables.

Results. No significant associations were found between reward-related activation and mood symptoms at baseline. An association was found between baseline reward-related activation in the ventral striatum and mood symptoms at follow-up despite the absence of such an association at baseline. Enhanced sensitivity to anticipation of rewards at age 14 significantly predicted lower (hypo)manic symptoms at age 22. Enhanced sensitivity to anticipation of rewards at age 14 predicted lower depressive symptoms at age 22, however, this did not reach statistical significance.

Conclusion. Our findings provide some evidence that blunted anticipatory reward profiles predict future increases in mood symptoms. These findings may suggest that vulnerability to BSD may be conferred by a need to compensate for intrinsic reward hyposensitivity by seeking out higher levels of reward in situations of higher risk.

1. Introduction

1.1. Bipolar Spectrum Disorder

Bipolar spectrum disorder (BSD) represent a spectrum of mood disorders that are characterised by episodic fluctuations in mood states, including intermittent episodes of depression, mania and euthymia, each of which are accompanied by respective changes in emotional and motivation processes (American Psychiatric Association, 2013). BSD has a high recurrence and disability rates, substantial disease and economic burden, and a suicide risk that is twenty times higher than that in the general population (Deckersbach et al., 2016; Simon et al., 2007). It is the leading cause of premature mortality and functional impairment, despite comparatively low prevalence rates, and is associated with substantial health care costs (World Health Organisation, 2017). BSD may be better understood as a spectrum that ranges from subclinical to clinical manifestations of symptoms and impairment. This spectrum is characterised by both trait and state dysregulation of affect, cognition, and behaviour (Sperry & Kwapil, 2017). BSD is highly heritable, with estimates exceeding 80.5% (Kieseppä et al., 2004). However, although it appears as though BSD diagnosis is highly heritable, there are substantial genetic correlations between hypomanic and manic (hereafter known as (hypo)manic) and depressive symptoms, indicating that there is significant heritability at the symptom level in BSD (McGuffin et al., 2003). This suggests a role for physiological mechanisms underlying symptoms, likely including neurobiological mechanisms. The reward system has been suggested as a viable mechanism, given the involvement of the reward system in mood and motivated or goal-directed behaviour and the observations BSD symptoms can include excessive pleasure-seeking and increased impulsivity (Reddy et al., 2014), and risk-taking (Miskowiak et al., 2019), and anhedonia (Satterthwaite et al., 2015). Clinical observations such as these have led to the proposal that BSD results from

dysregulation of reward-related networks that underlie motivational processing and goal-directed behaviour (Johnson, 2005b; Miller, 1993).

1.2. Reward Processing and BSD

Reward sensitivity refers to the level of an individual's approach motivation and responsiveness towards goals and rewards (Alloy, Bender, et al., 2012; Gray, 1994). One of the most well-established theories of BSD is the reward hypersensitivity model, which argues that BSD are characterised by increased reactivity to goal- and reward-relevant cues (Alloy et al., 2016; Depue & Iacono, 1989; Depue et al., 1987; Johnson, 2005a; Johnson et al., 2012). This model can account for both manic and depressive episodes in BSD; reward-activation stimuli (internal or external) can result in excessive approach-related affect, behaviour and motivation, and ultimately result in (hypo)manic symptoms e.g., increased risk-taking. Conversely, reward-deactivation events can lead to excessive down-regulation of approach-related affect, behaviour and motivation which can result in depressive symptoms e.g., anhedonia. Thus, a hypersensitivity to internal or external cues signalling potential gain or loss of reward, and a tendency towards excessive activation and deactivation of the reward system confer a vulnerability to the development of BSD (Alloy & Nusslock, 2019).

1.3. Behavioural Evidence for Reward Hypersensitivity Model of BSD

There is considerable theoretical and empirical support for the reward hypersensitivity model (Alloy et al., 2015; Alloy et al., 2016; Nusslock & Alloy, 2017). Briefly, individuals with or at high risk for BSD report greater self-reported, behavioural, emotional, and cognitive responses to rewards, compared to healthy controls (see Nusslock & Alloy, 2017 for a review). Individuals with BSD have shown elevated self-reported reward sensitivity

and increased incidence of reward-relevant personality traits (Johnson et al., 2012; Johnson et al., 2009; Meyer et al., 2001). These self-reported measures of reward hypersensitivity remain elevated even after remission of manic symptoms (Meyer et al., 2001). Additionally, increased reward sensitivity has been shown to predict the onset of BSD (Alloy et al., 2008; Alloy, Bender, et al., 2012), development of more severe subtypes of BSD (Alloy, Urošević, et al., 2012) and is associated with clinical severity and impairment in BSD (Meyer et al., 2001). Elevated behavioural approach sensitivity, assessed on the Behavioural Inhibition System and Behavioural Approach System scales, has also been shown to persist into euthymic phases in BSD and predict healthy controls' transition to BSD (Alloy, Bender, et al., 2012; Fletcher et al., 2013; Meyer et al., 2001). This suggests that reward hypersensitivity may be a putative endophenotype and vulnerability marker for BSD. Therefore, the above evidence supports the suggestions that reward hypersensitivity is central to the development and symptom trajectory in BSD. However, it is important to note that self-reported measures are subject to response biases and as such, it is crucial to complement the above findings with investigations of correlates of reward hypersensitivity on a more objective, neurobiological level. This is in line with recent efforts such as the Research Domain Criteria (RDoC) (Insel et al., 2010), which is a National Institute of Mental Health initiative to address the challenges of using current psychiatric categories as phenotypes for psychopathology research. The RDoC seeks to characterise the mechanisms across biopsychosocial dimensions that underlie psychiatric disorders to further our understanding of how these are altered in psychopathology (Krueger & DeYoung, 2016). This is crucial when attempting to locate potential vulnerability markers in individuals who may be at risk of developing BSD but who do not yet display the behavioural phenotype. Thus, research over the past two decades has explored whether the reward

hypersensitivity that has been observed in psychological and behavioural measures is reflected in the neural reward system (Johnson et al., 2012).

1.4. The Reward System

Over two decades of neuroimaging research has consistently implicated neural activity in regions that receive mesocorticolimbic dopamine projections in reward processing and have identified two distinct components of reward processing: anticipation and receipt (McClure et al., 2004; Oldham et al., 2018). Evidence to date suggests that the neural reward system consists of a highly complex, interconnected network of fronto-subcortial regions (Haber & Knutson, 2010). These regions are associated with reward salience, reward learning and positive affect, process both internal and external reward-related stimuli, and predict the probability of future rewards based on previous experiences (Haber & Knutson, 2010; Schultz & Dickinson, 2000). Two fundamental regions in this fronto-subcortical circuit are the ventral striatum (VS) and the orbitofrontal cortex (Diekhof et al., 2012). The VS primarily supports reward encoding and anticipation, and prediction error signalling (Dillon et al., 2008; Knutson et al., 2005), whilst the orbitofrontal cortex is involved in encoding reward values, comparing values of different stimuli, and assessing the probability of reward receipt (McDannald et al., 2011). Other regions involved in the reward circuit include the ventral tegmental area, substantia nigra, anterior cingulate cortex, amygdala, ventral pallidum, dorsal striatum, raphe nuclei, lateral habenula nucleus, and dorsolateral, ventromedial and ventrolateral prefrontal cortex (Haber & Knutson, 2010). These regions interact via dopaminergic pathways to form the fronto-striatal reward system, which regulates anticipatory and consummatory reward processing to facilitate drive motivation, and goal-directed and approach behaviour in the presence of reward signals (Berridge & Robinson, 1998, 2003). Researchers can investigate

this system by observing neural responses during reward-related tasks, which involve the presentation and omission of reward stimuli (Bart et al., 2021). Researchers typically employ monetary incentives in these tasks, as this enables researchers to control for potential confounding factors related to arousal, salience, attention and motor demands, and further, to directly contrast neural responses to anticipation and receipt of gains and losses (Lutz & Widmer, 2014). One such task is the Monetary Incentive Delay (MID) task (Knutson et al., 2001). This task offers individuals an opportunity to either gain or lose a reward of differing magnitude e.g., £0.00, £0.50. Individuals will gain or lose the reward depending on how quickly they respond to a target. The MID task can be used to study the distinct phases of: reward anticipation, which is conceptualised as the period of the task when individuals are awaiting feedback of gain or loss; and reward receipt, which is conceptualised as the period of the task when individuals have received feedback of gain or loss (Knutson et al., 2001). Numerous studies have used reward related tasks such as the MID and other similar tasks to investigate reward-related neural responses in the context of BSD (Lutz & Widmer, 2014).

1.5. Neuroimaging Evidence for Reward Hypersensitivity Model of BSD

Neurobiological and neurophysiological literatures have provided additional support for the reward hypersensitivity model of BSD. Elevated left frontal electroencephalogram (EEG) activity has been linked with elevated approach behaviour, response bias to reward-related cues, and self-reported reward sensitivity (Coan & Allen, 2004). This elevated EEG activity has further been observed in individuals prone to hypomania and individuals with a diagnosis of BSD (Harmon-Jones et al., 2008; Mason et al., 2012). Similarly, structural Magnetic Resonance Imaging (MRI) studies have reported abnormalities in prefrontal and striatal volumes in individuals who are at-risk for or currently have a BSD diagnosis (McDonald

et al., 2004). Conversely, functional MRI (fMRI) studies have provided mixed support for the reward hypersensitivity model of BSD (see Nusslock & Alloy, 2017 for a review). For example, studies using reward-based paradigms have reported elevated activation in the VS and the orbitofrontal cortex in individuals with BSD (see Alloy et al., 2016; Nusslock & Alloy, 2017 for reviews). Therefore, there appears to be some evidence supporting a relationship between BSD and elevated activation in the fronto-striatal reward circuit, however, there are inconsistent findings for striatal activation; some studies have reported increased activation (Dutra et al., 2015; Nusslock et al., 2012; Singh et al., 2013), some have reported decreased activation (Abler et al., 2008; Johnson et al., 2019), and still others have reported no difference between BSD and healthy controls (Bermpohl et al., 2010). Studies using at-risk populations have reported similarly inconsistent findings. For example, using the MID task, Singh et al. (2014), reported decreased activation in and connectivity between reward-related regions during anticipation of loss and greater activation in orbitofrontal cortex during reward receipt, whereas other studies that employed a card-guessing task found elevated connectivity between striatal and prefrontal regions during reward receipt (Manelis et al., 2016; Soehner et al., 2016). Therefore, although there is evidence for the presence of elevated neural activity in the front-striatal reward circuit in BSD, there are contradictory findings regarding VS activity. Furthermore, it is as yet unclear if reward hypersensitivity in the fronto-striatal reward circuit constitutes a trait vulnerability to BSD (Bart et al., 2021).

A number of factors may help to explain these discrepant findings. Firstly, studies of clinical populations of BSD typically categorise participants as being in euthymic, manic or depressive episodes. However, the dimensions of (hypo)manic and depressive symptoms have been shown to co-occur and fluctuate relatively independently of each other within BSD (Johnson et al., 2011), with mixed affective states being more commonly present than not

(Broome et al., 2015). Relatedly, whilst unipolar depression appears to be characterised by reward hyposensitivity, there is debate regarding the mechanism underlying bipolar depression (Alloy et al., 2016). The reward hypersensitivity model argues that reward hypersensitivity underlies risk for both (hypo)manic and depressive symptoms due to a hypersensitivity to cues signalling the attainment and loss of rewards, and to these events themselves (Depue et al., 1987; Urošević et al., 2008). However, it may be that different aetiological mechanisms underlie bipolar depression, such as reward hyposensitivity as is the case in unipolar depression. Thus, (hypo)manic and depressive symptoms may have opposing or independent relationships with reward processing. However, existing studies may not have had sufficient power to tease apart this relationship (Alloy & Nusslock, 2019). Secondly, clinical populations of BSD are typically in receipt of antidopaminergic medications. As dopamine is a key neurotransmitter in the reward system, medications which regulate its transmission may result in neural adaptations within the reward system, which may explain discrepant findings (Mason et al., 2012; Phillips et al., 2008). Furthermore, the majority of studies have examined populations with a prolonged course of BSD. This chronicity of BSD and associated secondary confounds such as repeated exposure to mood episodes, increased incidence of hospitalisations, heightened medication load, and accumulating social and occupational dysfunction may further help to explain conflicting findings (Bart et al., 2021). Finally, differences in methodology may limit the comparability of results; for example, some studies utilized a card-guessing fMRI paradigm, which includes a decision-making component, whereas others utilized the monetary incentive delay fMRI, where only a button press to a target is required. Thus, regions within the neural reward circuitry may be differentially activated depending on the paradigm utilized in a given study and the different processes they recruit (Bart et al., 2021).

1.6. Aims and Hypotheses

The current study seeks to address each of the above issues by examining the relationship between reward processing and (hypo)manic and depressive symptoms longitudinally in a large (N > 1500) community-based sample, using a MID fMRI paradigm. This study will examine the relationship between subthreshold (hypo)manic and depressive symptoms, and reward-related neural responses. We will examine (hypo)manic and depressive symptoms simultaneously, rather than classifying participants as being in distinct and disparate episodes, so as to assess the independent contributions of both (hypo)manic and depressive symptoms to reward-related neural responses. Moreover, this study will utilize a preclinical population to minimize the impact of disorder chronicity and antidopaminergic medication. Given that previous research has highlighted the important role of the VS in reward processing in general (Diekhof et al., 2012), and this region has also been the focus of the extant literature examining reward processing in BSD (see Bart et al., 2021 and Nusslock and Alloy, 2017 for a review), this study will employ a region-of-interest approach focusing on this region.

The current study's included variables, research questions and hypotheses, and planned analyses were preregistered on Open Science Framework (https://osf.io/8bue5) prior to any data being downloaded or analysed. In summary, we seek to address two core research questions:

- Are depressive and (hypo)manic symptoms independently associated with baseline reward responses?
- Do baseline reward responses predict intensification of mood symptoms longitudinally?

In relation to the first research question, two opposing hypotheses may account for an association between reward-related neural responses and mood symptoms. This study will seek to adjudicate between these two hypotheses. Thus, this study will explore whether depressive and (hypo)manic symptoms (independent variables) are associated with baseline reward response (dependent variable), and whether this association is accounted for by either H1 or H2 such that:

H1: Depressive symptoms are associated with blunted reward-related striatal activation (H1a) and (hypo)manic symptoms are associated with elevated reward-related striatal activation (H1b) i.e., there is a double dissociation between mood symptoms and neural activation in the VS during reward anticipation.

H2: Individuals who experience both depressive and (hypo)manic symptoms i.e., are at risk for BSD, will show elevated reward-related striatal activation i.e., the interaction between depressive and (hypo)manic symptoms will be associated with elevated neural activation in the VS during reward anticipation.

Secondly, this study will explore whether baseline reward-related responses (independent variable) predict intensification of mood symptoms longitudinally (dependent variables) such that:

H3: Neural activation during reward anticipation in the VS at baseline will predict increases in depressive and (hypo)manic symptoms at follow-up. This association will remain significant when controlling for baseline level of mood symptoms.

2. Methods

2.1. Design

This study is a secondary analysis of behavioural and fMRI data from the IMAGEN study of adolescent development. This is a longitudinal study of community-based adolescents and their parents. Baseline assessments were conducted at 14 years, using a combination of home assessments and study-centre visits in which adolescents completed self-report and interview measures, in addition to structural and fMRI scans whilst completing several different tasks. Clinical follow-up assessments were conducted at 16, 19 and 22 years, and structural and fMRI follow-up assessments were conducted at 19 and 22 years. The present study will use data from the first and last waves of the IMAGEN study and will focus on the Monetary Incentive Delay task and depression and bipolar symptoms which are described in detail below.

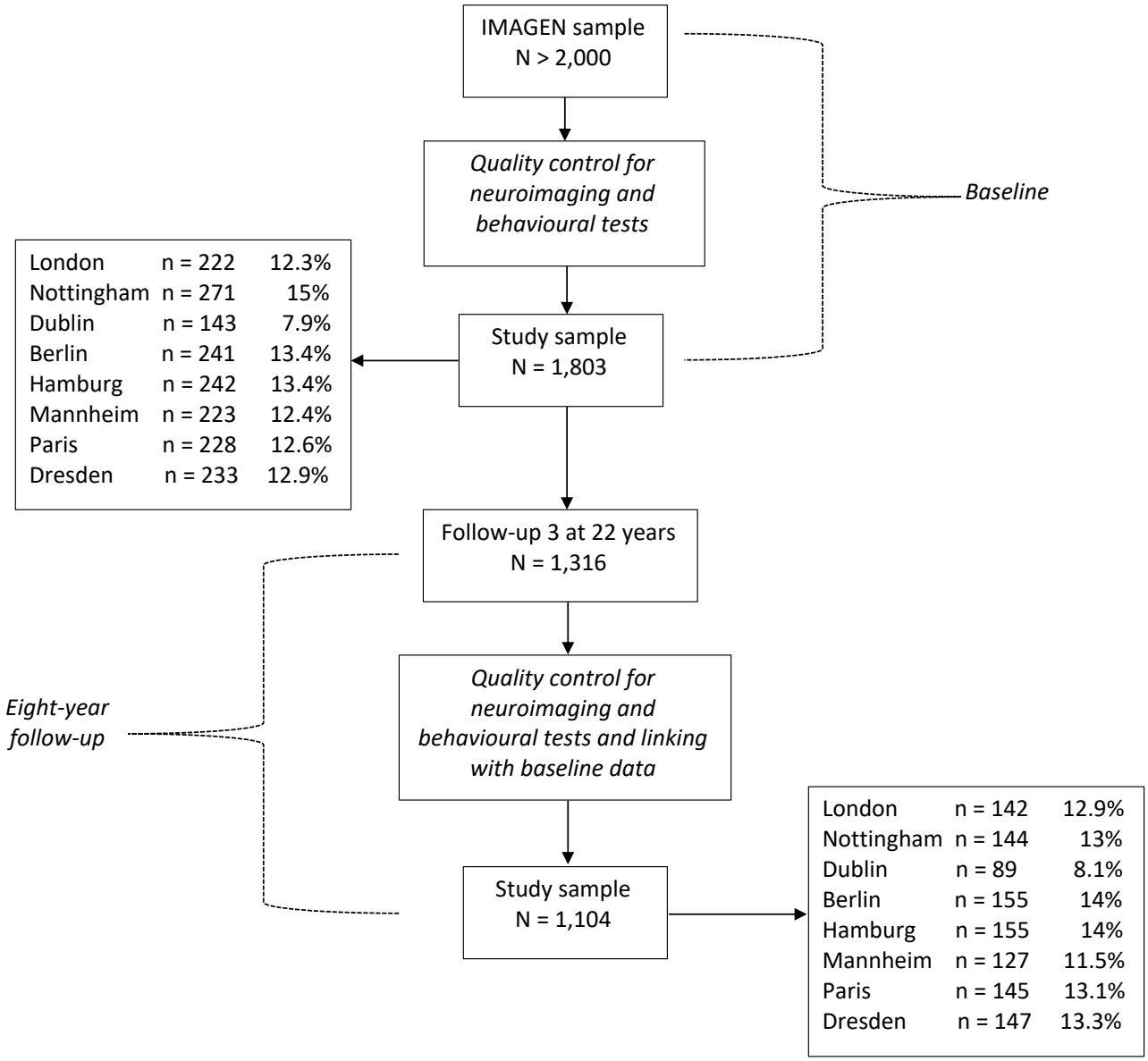
2.2. Power Analysis

Power analysis was informed by Stringaris et al.'s (2015) study, which examined reward-based striatal activation and depression. Using the same dataset and task, this study found an association between reward-related striatal activation during reward anticipation and depressive symptoms, with an effect size of *Cohen's d* = 1.03. This was used to determine the implied power in the current study. A power analysis using G*Power (Faul et al., 2007) based on the effect size (d = 1.03) with alpha set at 0.05, suggests that with n = 1803 and 11 predictor variables, this study would have 99.9% power to detect an effect.

2.3. Participants

Adolescents and their parents were recruited via high schools in eight sites across Europe. Sampling approaches were implemented to ensure maximization of ethnic homogeneity and diversity in terms of socioeconomic status, academic achievement, and behavioural/emotional functioning. Ethical approval was granted by all local ethics committees and written informed consent was provided by all participants and legal guardians of each participant and verbal assent was obtained from adolescents. A detailed description of study recruitment and assessment procedures has been previously published (Schumann et al., 2010), and are also described in the Standard Operating Procedures for the IMAGEN project (https://imagen-europe.com/resources/standard-operating-procedures/). Participants were included in the current study if they had data available for key measures at baseline and at baseline and follow-up assessments. Further, participants who did not complete the relevant fMRI task (described below), who did not have scanner motion data nor neural activation data for reward anticipation, and whose neuroimaging values fall outside three standard deviations of the average were excluded. After quality control for neuroimaging and behavioural measures, 1,803 adolescents were included in the study of which 1,104 had data available at follow-up (Figure 1).

Figure 1. CONSORT Diagram of participants from baseline through to follow-up



2.4. Procedure

All participants completed questionnaires before fMRI scanning and performed a Monetary Incentive Delay Task (detailed bellow) during scanning.

2.5. Clinical Measures

Development and Well-being Assessment Interview (DAWBA; Goodman, Ford, Richards, Gatward, & Meltzer, 2000; http://www. dawba.info).

This is a computer-based package that assesses presence and frequency of psychiatric symptoms and resultant impact and generates ICD-10 and DSM-IV psychiatric diagnoses for 5-16-year-olds. This measure is designed to maintain consistency across cultural and language groups; as such, diagnoses are made by clinical raters who have received common trainings and take part in frequent cross-language training and consensus meetings. The current study used the depressive and (hypo)mania subscales of the DAWBA. Parents and adolescents are presented with screening questions to which they have the option of answering, no*, a little, or a lot*. If they answer, "*a little"* or "*a lot*", interviewers subsequently enquire whether the individual has experienced specific symptoms of psychiatric disorders. For each individual symptom, participants again have the option of answering *no, a little, or a lot*. Answers to these questions are coded for as "No" = 0, "A little" = 1, and "A lot" = 2. For each participant, their depressive and (hypo)manic symptom score was calculated by summing the relevant questions.

Temperament and Character Inventory (TCI; Cloninger, Przybeck, Svrakic, & Wetzel, 1994):

This is a 240-item, self-report measure that assesses four temperament and three-character dimensions. The temperament dimensions measure individual differences in harm avoidance, novelty seeking, reward dependence, and persistence. The current study included the Total Novelty Seeking score at baseline in analyses, which is the sum of scores on all subscales, due to their relevance to BSD.

Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2003):

The WISC-IV is designed to assess cognitive ability in children and adolescents in five composite areas: i) Verbal Comprehension; ii) Perceptual Reasoning; iii) Working Memory; iv) Processing Speed; Full Scale IQ. The short form was used in the IMAGEN study, which included the subsets: i) Similarities; ii) Vocabulary; iii) Matrix Reasoning; iv) Block Design and v) Digit Span Forward. The current study used a sum of these subtests as an estimate for cognitive functioning, in line with previous research (Büchel et al., 2017).

Puberty Development Scale (PDS; Carskadon & Acebo, 1993):

This provides an eight-item self-report measure of physical development based on the Tanner stages. The measure has separate forms for males and females. Participants answer questions about their growth in stature and pubic hair, as well as menarche in females and voice changes in males. The current study included the mean PDS score at baseline in analyses.

European School Survey Project on Alcohol and Drugs (ESPAD; Hibell et al., 1997):

This was used to capture each participant's use of cigarettes, alcohol and illicit drugs. With respect to cigarettes, a score indexing daily use will be used where 0: 'not at all'; 1: 'less than 1 cigarette per week'; 2: 'less than 1 cigarette per day'; 3: '1-5 cigarettes per day'; 4: '6-10 cigarettes per day'; 5: '11-20 cigarettes per day'; and 6: 'more than 20 cigarettes per day'. With respect to alcohol use, a score indexing monthly use will be used where 0: '0 drinks per month'; 1: '1-2 drinks per month'; 2: '3-5 drinks per month'; 3: '6-9 drinks per month'; 4: '10-19 drinks per month'; 5: '20-39 drinks per month'; and 6: '40 or more drinks per month'. With

respect to illicit drugs, a score indexing lifetime use of marijuana, glue/aerosols, tranquilisers, amphetamines, LDS, hallucinogens, crack, cocaine, relevin, heroin, narcotics, ecstasy, ketamine, GHB/liquid ecstasy, and anabolic steroids will be used where : 0: '0'; 1: '1-2'; 2: '3-5'; 3: '6-9'; 4: '10-19'; 5: '20-39'; and 6: '40 or more'.

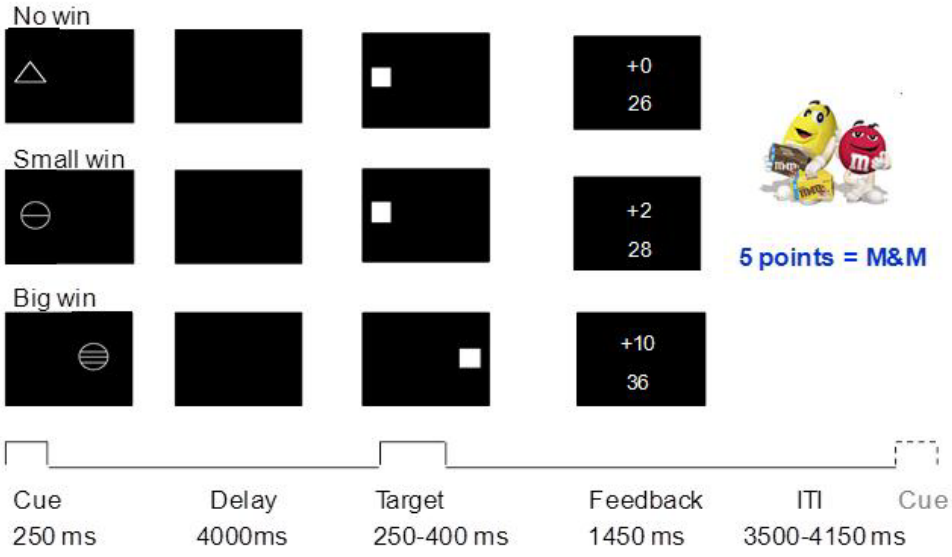
2.6. MID Task

The IMAGEN study utilised a modified version of the monetary incentive delay task, adapted from Knutson, Adams, Fong & Hommer, (2001), to investigate neural activity during reward processing. The task includes anticipation and feedback phases of three reward magnitudes (Large-Win, Small-Win, and No-Win). The task consisted of 66 ten-second trials. In each trial, participants were presented with sequences of cues and targets and a feedback phase. Cues (250ms) signalled the onset of the trial and reliably indicated the position of the target, in addition to the possible amount of points the participants could win. Cues included a triangle (0 points), or a circle with one line (2 points), or a circle with two lines (10 points). After a variable delay (4000 – 4500ms) of fixation on a white crosshair, participants must respond when the target (a square) is presented randomly on screen, by pressing a button with their right or left index finger to indicate whether the target appeared on the left- or right-hand side of the screen. If participants responded while the target was on the screen, they received the points, but if they responded before or after the target's disappearance, they received no points. Participants received feedback 1450ms after their response about the win or loss of the trial and how many points won. Task difficulty was adjusted using a tracking algorithm to ensure that each participant successfully responded on approximately 66% of trials. Participants completed a practice session for approximately five minutes outside the scanner, at which point they were informed that at the end of the sessions, they

would receive one sweet for every five points at the baseline sessions, or a small amount of money at the follow-up sessions. Functional magnetic resonance imaging (fMRI), blood oxygen-level dependent (BOLD) responses were measured during reward anticipation and reward outcome. Task presentation and recording were conducted using the Visual Basic 2005 with .NET Framework Version 2.0, and the visual and response group system from Nordic Neuro Lab (NordicNeuroLab AS, Bergen, Norway).

Figure 2.

Outline of Stages of Monetary Incentive Delay Task. (Stringaris et al., 2015)



Note. The current study analysed neural responses during the large reward versus no reward contrast

2.7. fMRI Data Acquisition

Data was acquired on 3T whole-body magnetic resonance scanners from multiple manufacturers (Siemens, Philips, General Electric and Bruker) across several research centres. The same scanning protocol was used in all sites. Data are stored centrally at the Neurospin centre (Paris). High-resolution T1-weighted 3D structural images were acquired for

anatomical localisation and co-registration with the functional time-series. For fMRI images, a gradient-echo, echo-planar T2*-weighted pulse sequence was used to acquire 300 volumes with 40 slices (2.4mm slice thickness with 1mm gap) acquired in descending order for each volume for each participant. The time to repetition for volume acquisition was set to 2,200ms and the time to echo to 30ms, to ensure reliable imaging of subcortical areas. In-plane resolution was 64 x64 with a field of view of 220 x 220 mm. The plane of acquisition was tilted to parallel the anterior-posterior commissure line. For anatomical reference, a 3D magnetisation prepared gradient-echo sequence of the whole brain was obtained with time to repetition of 6.8ms and a time to echo of 3.2ms. These neuroimaging parameters were selected to ensure comparability of data across different scanners and study sites. See Schumann et al. (2010) for further details of image acquisition protocols and quality control procedures.

2.8. Statistical fMRI Parametric Analyses

Pre-processing and single subject statistical analysis were performed by the consortium using SPM12 (Statistical Parametric Mapping: Wellcome Department of Cognitive Neurology, London, UK). Spatial pre-processing included: slice time correction, realignment to first volume, non-linearly warping to a custom EPI template generated by an average of the mean images of the first 552 study participants, resampling at a resolution of $3x3x3mm^3$ and smoothing with an isotropic Gaussian kernel of 5mm FWHM. Single-subject statistical models analysed the resliced data using the following regressors: i) anticipation of large gain; ii) anticipation of small gain; iii) anticipation of no gain; iv) feedback indicating large gain; v) feedback indicating small gain; vi) feedback indicating no gain. Each regressor was defined separately for successful and unsuccessful response trials i.e., 'hits' and 'misses. Thus, each

model, included a total of 12 orthogonal regressors. Trials in which participants failed to respond were modelled similarly but separately as error trials. Estimated movement was added to the design matrix in the form of 21 additional covariate regressors; 12 motion regressors (3 translations, 3 rotations, 3 translations shifted 1TR before, and 3 translations shifted 1TR later) and 9 additional columns corresponding to the long-term effects of the movement (3 nuisance variables for white matter and 6 nuisance variables for ventricles). Regressors modelling experimental conditions were convolved using SPM's default Hemodynamic Response Function. Estimated model parameters were linearly combined to create contrast maps, significance maps and maps of the residual variance of the model, all of which are provided by the IMAGEN consortium (Schumann et al., 2010). The current study analysed neural responses during anticipation of large rewards versus no reward, so as to focus on exploring whether a relationship exists between mood symptoms and altered reward processing, rather than exploring whether there are differences in sensitivity to or discrimination between large and small rewards. This is in line with prior research examining neural activation during anticipation of rewards (Berghorst et al., 2016; Dutra et al., 2015; Johnson et al., 2019; Kollmann et al., 2017; Schreiter et al., 2016; Yip et al., 2015). The regression coefficients (beta-weights) from the first level model will be used in whole-brain and regions of interest analyses (ROI) described below.

2.9. ROI Analyses

To examine whether reward-related activation in the VS is associated with mood symptoms, we conducted ROI analyses in this region. ROI analyses are a well-established approach to fMRI analysis when there are well-defined a priori regional predictions of task-related activation based on prior research (Poldrack, 2007). Whole-brain analyses require

stringent corrections for multiple comparisons; whereas these corrections are necessary when there are no a priori regional predictions, these corrections are overly conservative when these do exist. ROI analyses restrict the number of statistical tests, thus controlling for Type I errors and limiting the need for stringent corrections for multiple comparisons (Poldrack, 2007).

MarsBaR SPM toolbox (http://marsbar.sourceforge.net/) was used to generate a spherical bilateral VS ROI mask (Figure 2). Spherical (12mm diameter) ROIs were centred on Montreal Neurological Institute coordinates -12, 14, -8, and 12, 14, -8, which are the activation peaks identified by a previous study using the IMAGEN data to identify neural activation during anticipation of rewards in the MID task (Cao et al., 2019). ROI within-group activations were calculated using one-sample t-tests, with a cluster corrected $p < 0.05$ family wise error rate. The fMRI signal (beta estimates) across voxels in these ROIs for each participant were extracted for the contrast of interest (anticipation of large reward versus no reward) using MarsBaR SPM toolbox (http://marsbar.sourceforge.net/) and exported to Statistical Package for the Social Sciences (SPSS) for further analyses.

To answer H1 and H2, the activations in the VS ROIs at baseline were analysed for associations with mood symptom (depressive and (hypo)manic) score at baseline using a multiple regression analysis. A linear mixed-effects model was used with the beta-weights for anticipation of large reward versus no reward in bilateral VS as the outcomes and depressive symptom score and (hypo)manic symptom score as the main predictors. To answer H2, an interaction term was further added to the model as a predictor. The interaction term was created by multiplying the depressive and (hypo)manic symptom scores for each participant. Site ID, biological sex at birth, age, pubertal status, substance and alcohol use, and trait

novelty seeking were included as covariates. The significance threshold for the multiple regression ROI analyses was $p < 0.05$.

To answer H3, a multiple regression analysis was further conducted to investigate if there is a longitudinal association between the activation of VS ROIs measured at baseline (14 years) and depression and (hypo)manic symptoms measured at follow-up (22 years). A linear mixed-effects model was conducted in SPSS with the follow-up depression and (hypo)manic score as the outcome, and the beta-weights for anticipation of large-no reward in bilateral VS at baseline as the main predictors. Site ID, biological sex at birth, age, pubertal status, substance and alcohol use, trait novelty seeking, and baseline depression and (hypo)manic symptom scores were included as covariates. The significance threshold for the multiple regression ROI analyses was $p < 0.05$.

2.10. Exploratory Whole-brain Analyses

Whole-brain within-group activations were calculated using one-sample t-tests, with a cluster corrected $p < 0.05$ family wise error rate.

2.11. Normality and Multicollinearity Checks

To evaluate whether assumptions of normality for parametric testing were met, the normality of continuous demographic, clinical and neuroimaging data were verified using the Shapiro-Wilk test and a skewness and kurtosis of between +- 1.00. Absence of multicollinearity was verified using tolerance of greater than 0.1 and a Variance Inflation Factor of less than 5.00.

3. Results

3.1. Demographic Characteristics

Longitudinal data of 1803 White adolescents at baseline (1104 of whom were available as young adults at follow-up) was included in the current study. Participant demographic data is presented in Table 1.

Table 1.
Participant Demographics and Characteristics

	Baseline (age 14) (*n* = 1803)	**Follow-up (age 22) (*n* = 1104)**
Age, Mean (*SD*)	13.96 (*0.46*)	22.04 (*0.68*)
Female, n (%)	916 (50.8%)	583 (52.8%)
Socioeconomic status composite, Mean (*SD*)	-5.29 (*4.22*)	2.15 (*2.38*)
Centre site, **n** (%)	**222** London (12.3%) **271** Nottingham (15%) **143** Dublin (7.9%) **241** Berlin (13.4%) **242** Hamburg (13.4%) **223** Mannheim (12.4%) **228** Paris (12.6%) **233** Dresden (12.9%)	**142** London (12.9%) **144** Nottingham (13%) **89** Dublin (8.1%) **155** Berlin (14%) **155** Hamburg (14%) **127** Mannheim (11.5%) **145** Paris (13.1%) **147** Dresden (13.3%)
Currently taking psychotropic medication[b], n (%)	36 (2%)	
DAWBA depression subscale score, Mean (*SD*)	3.75 (*6.51*)	3.27 (*7.12*)
DAWBA (hypo)manic subscale score, Mean (*SD*)	15.44 (*16.18*)	7.32 (*12.96*)
PDS score[b], Mean (*SD*)	2.69 (*0.45*)	
Intelligence[a] Estimate[b], Mean (*SD*)	93.82 (*20.93*)	
TCI novelty seeking score[b], Mean (*SD*)	111.54 (*10.34*)	
ESPAD alcohol use in last 30 days[b], Mean (*SD*)	0.6 (*0.95*)	
ESPAD daily cigarette use[b], Mean (*SD*)	0.6 (*0.44*)	
ESPAD lifetime illicit drug use[b], Mean (*SD*)	0.31 (*2.36*)	

Note. DAWBA: Developmental and Well-Being Assessment Interview; TCI: Temperament and Character Inventory; PDS: Pubertal Development Scale; ESPAD: European School Survey Project on Alcohol and Drugs

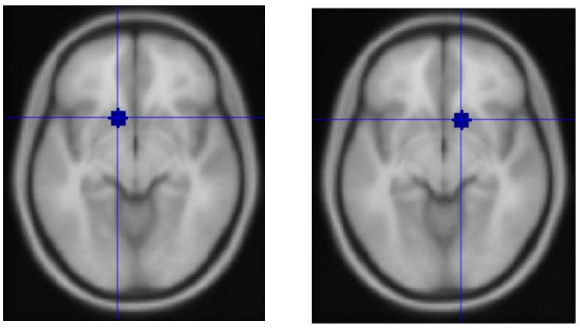
[a]Intelligence reflects the sum of the following subscales of the Weschsler Intelligence Scale for Children (WISC-IV): Similarities, Vocabulary, Block Design, Matrix Reasoning, Digit Span Forward.
[b]Data not available at follow-up

3.2. Functional Neuroimaging Data

Figure 2a illustrates the mask used for ROIs in the VS during the reward anticipation phase of the MID task for the participants at ages 14. As stated in the Methods section, this mask was centred on the *x, y, z* coordinates *-12, 14, -8; 12, 14, -8*, which is the Nucleus Accumbens area in the VS. A first confirmatory voxel-wise analyses contrasted whole-brain activity during anticipation of large reward versus no reward across all participants to verify main effects of reward anticipation at age 14. Across all participants, large versus no reward anticipation elicited expected increases in activity in mesolimbic regions including the striatum (n = 1803; peak *x, y, z*: 12 -1 13mm, $T = 34.45$, $p < .000$, corrected t-test; -12 -1 13mm, $T = 28.73$, $p < .000$, corrected *t*-test; Figure 2b). The mask that we employed falls within this region.

Figure 3.
Localisation of the Ventral Striatum (VS)

a

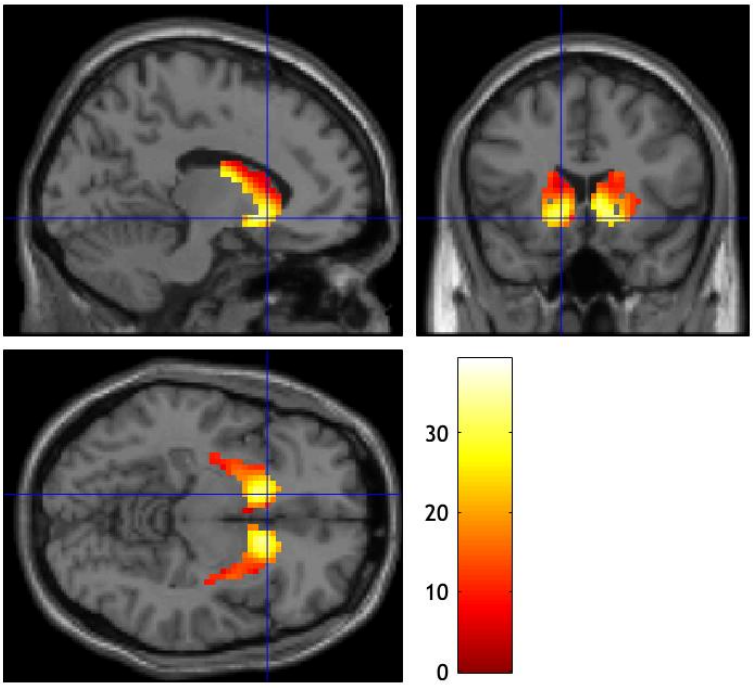


Left
x, y, z: -12, 14, -8

Right
x, y, z: 12, 14, -8

2a The masks used in the current study for the VS.

b



2b fMRI activity in striatal area during anticipation of large reward versus no reward at age 14 (*n* = 1803). Overlaid on a mean structural magnetic resonance scan showing a sagittal (left), coronal (right), and axial (bottom) section, activation display threshold is $p < .05$ (FWE-corrected, *t*-test).

3.3. Association of Depressive and (Hypo)Manic Symptoms with Baseline Reward Neural Response (Hypothesis 1 and Hypothesis 2)

To answer our cross-sectional hypotheses, we tested whether a) Depressive symptoms are associated with blunted striatal responses and (hypo)manic symptoms are associated with elevated striatal responses during reward anticipation (H1), and b) Individuals who are at risk for BSDs (experience both elevated depressive and (hypo)manic symptoms), will show elevated striatal responses during reward anticipation (H2), using multiple regression analyses. All data was assessed for normality and collinearity. A summary of the statistical findings for the multiple regressions for H1 and H2 analyses is presented in Table 2.

A multiple regression model did not identify any significant associations between the activations of the ROIs for the contrast of large win versus no win for the bilateral VS during reward anticipation and the depression and (hypo)manic symptom score, and the depression (hypo)manic symptom interaction term (Left VS: R^2 = .001, $F_{3, 1645}$ = .759, p = .517; Right VS: R^2 = .001, $F_{3, 1645}$ = .469, p = .704). Follow-up hierarchical multiple regressions further revealed that including other factors (age, gender, site ID, SES composite score, pubertal status, intelligence estimate, alcohol and drug use, and novelty seeking) in the model did not significantly alter the relationship between depression and (hypo)manic symptom score and depression (hypo)manic symptom interaction term and activation in the left and right VS at age 14, as shown in Table 2. However, adding age, gender, SES and site ID to the model significantly improved the model's prediction of activation in the left VS, $F_{10, 1635}$ = 1.887, p = .04. The final model accounted for approximately 1.7% and 1% of the variance of reward-related activation in left and right VS respectively. The results showed that site ID, specifically, the Dublin (03), Berlin (04) and Hamburg (05) sites were associated with activation in the left VS at age 14 (Table 2). Site ID (Dublin site, 03) was similarly associated with activation in the

right VS at age 14 (Table 2) but this model was not found to be significant, R^2 = .008, $F_{10, 1635}$ = 1.246, p = .256. See Figure 1 and Figure 2 in Appendix A for further illustration of these associations.

3.4. Association of Baseline Depressive and (Hypo)Manic Symptoms with Baseline Reward Neural Response Excluding Participants Taking Psychotropic Medication at Baseline

To explore whether the use of psychotropic medication was influencing the above findings, we performed the above analyses on a subsample of participants by removing participants who were taking psychotropic medication at age 14 (n = 968). This, similarly, did not alter the relationship between the activations in the bilateral VS and the depression and (hypo)manic symptom score depression (hypo)manic symptom interaction term: Left VS: R^2 = .002, $F_{3, 1610}$ = 1.147, p = .329; Right VS: R^2 = .001, $F_{3, 1610}$ = 0.626, p = .598 (See Appendix B for results of multiple regression analyses).

3.5. Association Between Depressive and (Hypo)Manic Symptoms at Baseline

To explore whether the confluence of depressive and (hypo)manic symptoms was influencing the above findings, a Pearson correlation coefficient was computed to assess the linear relationship between depressive and (hypo)manic symptoms at baseline (age 14). There was a significant positive correlation between the two variables, r(1801) = .307 , p < .001.

Table 2.
Results of Hierarchical Regression Analyses for the Activations of the Bilateral Ventral Striatum and the Depression Symptom Score, (Hypo)Manic Symptom Score and Depression (Hypo)Manic Symptom Interaction at Age 14.

	DV Reward-related activation (Left VS)			DV Reward-related activation (Right VS)		
	β	*t*	*p*	β	*t*	*p*
Step 1: Mood Symptoms						
Depression	-.042	-1.012	.312	-.016	-.387	.699
(Hypo)Manic	-.017	-.554	.58	.004	.133	.894
Interaction	.016	.343	.732	-.016	-.345	.730
	R^2 = .001, $F_{3, 1645}$ = .759 p = .517			R^2 = .001, $F_{3, 1645}$ = .469, p = .704		
Step 2: Demographics						
Depression	-.031	-.735	.463	-.013	-.298	.765
(Hypo)Manic	-.021	-.696	.486	.004	.117	.907
Interaction	.016	.333	.74	-.017	-.262	.717
Age	-.016	-.631	.528	-.004	-.169	.866
SES	.022	.861	.389	.001	.039	.969
Gender	.006	.256	.798	-.006	-.239	.811
ID_01	-.032	-1.009	.313	-.013	-.39	.696
ID_02	.013	.401	.688	.043	1.292	.197
ID_03	.059	1.995	**.046***	.081	2.71	**.007****
ID_04	.073	2.276	**.023***	.043	1.317	.188
ID_05	.064	1.98	**.048***	.053	1.644	.1
ID_06	.047	1.46	.144	.04	1.252	.211
ID_07	.017	.515	.607	.042	1.282	.2
	R^2 = .013, $F_{10, 1635}$ = 1.887 p = **.04***			R^2 = .008, $F_{10, 1635}$ = 1.246, p = .256		
Step 3: Non-Clinical Factors						
Depression	-.03	-.72	.471	-.013	-.306	.76
(Hypo)Manic	-.022	-.715	.475	.002	.051	.959
Interaction	.015	.32	.749	-.016	-.346	.729
Age	-.017	-.688	.491	-.007	-.294	.769
SES	.018	.716	.471	-.001	-.029	.977
Gender	.008	.309	.757	-.006	-.231	.817
ID_01	-.027	-.847	.397	-.011	-.348	.728
ID_02	.019	.573	.567	.044	1.3	.194
ID_03	.067	2.209	**.027***	.084	2.747	**.006****
ID_04	.077	2.393	**.017***	.044	1.351	.177
ID_05	.067	2.066	**.039***	.055	1.688	.092
ID_06	.051	1.575	.115	.041	1.26	.208

ID_07	.022	.671	.503	.045	1.359	.174
Pubertal Status	.012	.498	.618	.027	1.067	.286
Intelligence Estimate	.031	1.211	.226	.006	.225	.822
	R^2 = .014, $F_{2, 1633}$ = .843 p = .431			R^2 = .009, $F_{2, 1633}$ = .589, p = .555		
Step 4: Clinical Factors						
Depression	-.030	-.706	.48	-.014	-.329	.742
(Hypo)Manic	-.021	-.699	.485	.001	.025	.98
Interaction	-.017	.354	.723	-.017	-.354	.724
Age	-.015	-.614	.539	-.007	-.295	.768
SES	.017	.675	.5	-.001	-.057	.955
Gender	.01	.403	.687	-.005	-.207	.836
ID_01	-.026	-.816	.415	-.011	-.35	.726
ID_02	.019	.557	.578	.043	1.264	.206
ID_03	.066	2.161	**.031***	.085	2.765	**.006****
ID_04	.079	2.432	**.015***	.044	1.352	.177
ID_05	.068	2.093	**.036***	.055	1.693	.091
ID_06	.050	1.537	.124	.040	1.241	.215
ID_07	.027	.829	.407	.046	1.379	.168
Pubertal Status	.016	.630	.529	.025	.985	.325
Intelligence Estimate	.024	.949	.343	.005	.198	.843
Monthly Alcohol Use	.014	.527	.599	.023	.877	.380
Daily Cigarette Use	-.020	-.744	.457	-.008	-.277	.782
Lifetime Drug Use	-.052	-1.866	.062	-.009	-.307	.759
Novelty-Seeking	.019	.739	.46	.001	.042	.966
	R^2 = .017, $F_{4, 1629}$ = 1.512 p = .196			R^2 = 0.01, $F_{4, 1629}$ = .227, p = 0.924		

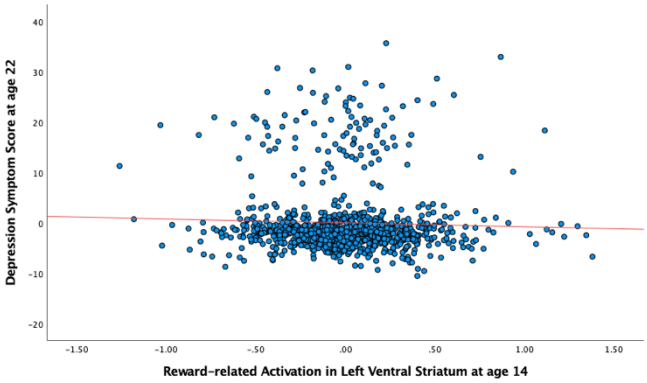
Note. All reported β estimates are standardized regression coefficients. n = 1649
New variables added in each step of model building are bolding to aid the reader.
ID_01: London; ID_02: Nottingham; ID_03: Dublin; ID_04: Berlin; ID_05: Hamburg: ID_06: Mannheim; ID_07: Paris
The VS activation was from the contrast of large-win vs. no-win.
VS, ventral striatum
$^{*}p < .05$
$^{**}p < .01$
Significant findings are bolded to aid the reader.

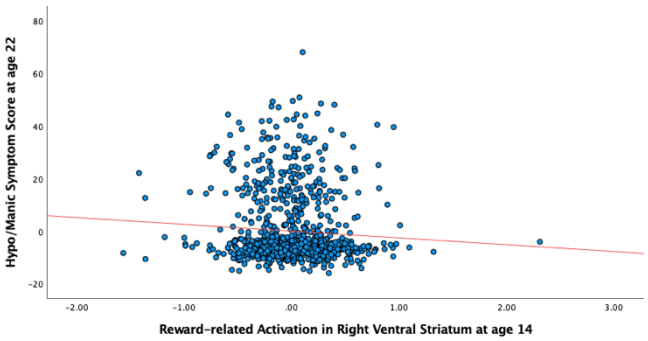
3.6. Prediction of Depressive and (Hypo)Manic Symptoms at Follow-up from Baseline Reward-related Neural Responses (Hypothesis 3)

To answer our longitudinal hypotheses, a multiple regression was carried out to investigate whether reward-related activation in the left and right VS at 14 years could significantly predict participants' depression and (hypo)manic symptom scores at age 22. The results of the regression indicated that the model was a significant predictor of depression score at 22 years, R^2 = .008, $F_{2, 981}$ = 3.764, p = .024. Although reward-related activation in the right and left VS at 14 years did not contribute significantly to the model: β = .002, p = .97 and β = -.089, p = .071, respectively (Table 3), activation in the left VS did approach significance (p = .07). As shown in Figure 4a, increased reward-related responses in the left VS at age 14 were associated with lower depression symptom scores at age 22. Further, follow-up hierarchical multiple regressions revealed that including other factors (age, gender, site ID, SES composite score, baseline intelligence estimate, baseline alcohol and drug use, baseline novelty seeking score and baseline mood symptoms at 14 years) altered this association, and it moved further away from significance (Table 3). Although there was no significant association found between reward-related activation in the left VS at age 14 and Depression Symptom score at 22, adding age, gender, SES, site ID, baseline intelligence estimate, baseline alcohol and drug use, baseline novelty seeking score and baseline mood symptoms to the model significantly improved the model's prediction of Depression Symptom Score at age 22, R^2 = .082, $F_{2, 964}$ = 12.593, p = <.001. The final model accounted for approximately 8.2% of the variance of Depression Symptom Score at 22 years. The results showed that site ID, specifically, the Nottingham (02) site, gender, baseline daily cigarette use, and baseline depressive symptom scores were associated with Depression Symptom score at age 22 (Table 3). See Figure 3 and Figure 4 in Appendix C for further illustration of these associations.

In contrast, the results of the multiple regression model indicated that the model was not a significant predictor of (hypo)manic score at 22 years, although it did approach significance, R^2 = .006, $F_{2, 981}$ = 2.936, p = .054. Although reward-related activation in the right VS at 14 years did contribute significantly to the model β = -.106, p = .030, activation in the left VS did not, β = .047, p = .343 (Table 3). Follow-up hierarchical multiple regressions revealed that including other factors (age, gender, site ID, SES composite score, baseline intelligence estimate, baseline alcohol and drug use, baseline novelty seeking score and baseline mood symptoms) did not alter this association, and the beta estimated for the reward-related activation in the right VS remained statistically significant, β = -.102, p = .038 (Table 3). As shown in Figure 4b, increased reward-related responses in the right VS at age 14 were associated with lower (hypo)manic symptom scores at age 22. Further, adding baseline mood symptoms to the model significantly improved the model's prediction of (hypo)manic Symptom score at age 22, $F_{2, 964}$ = 11.03, p < .001. The final model accounted for approximately 4% of the variance of (Hypo)Manic Symptom Score at 22 years. The results showed that baseline (Hypo)manic Symptom Score was associated with (Hypo)Manic Symptom score at age 22 (Table 3). See Figure 4 in Appendix C for further illustration of these associations.

Figure 4.
Partial Regression Plots of Mood Symptom Score at age 22 and Reward-related Neural Activation in Ventral Striatum at age 14.





4a Lower depressive symptoms at age 22 are associated with increased reward-related activation in left VS at age 14
Beta estimated for association between activation in left ventral striatum and depressive score approached significance.
β = -.089, *p* = .071

4b Lower (hypo)manic symptoms at age 22 are predicted by increased reward-related activation in right VS at age 14
Beta estimated for association between activation in right ventral striatum and (hypo)manic score was statistically significant.
β = -.106, p = .030

Table 3.
Results of Hierarchical Regression Analyses for the Reward-Related Activations of the Bilateral Ventral Striatum at Age 14 and the Depression Symptom Score and (Hypo)Manic Symptom Score at Age 22.

	DV Depression Symptoms (Age 22)			DV (Hypo)Manic Symptoms (Age 22)		
	β	*t*	*p*	β	*t*	*p*
Step 1: Reward-related VS activation (Age 14)						
Left-VS	-.089	-1.807	.071	.047	.949	.343
Right-VS	.002	.038	.970	-.106	-2.168	**.030***
	R^2 = .008, $F_{2, 981}$ = 3.764 **p = .024***			R^2 = .006, $F_{2, 981}$ = 2.936, *p* = .054		
Step 2: Demographics						
Left-VS	-.064	-1.313	.19	.036	.716	.474
Right-VS	-.014	-.293	.77	-.097	-1.959	**.050***
Age	.055	1.692	.091	.038	1.123	.262
SES	-.011	-.361	.718	-.007	-.229	.819
Gender	-.108	-3.43	**<.001*****	-.014	-.441	.659
ID_01	.090	2.126	**.034***	-.079	-1.838	.066
ID_02	.178	4.212	**<.001*****	-.040	-.927	.354
ID_03	.060	1.536	.125	-.055	-1.364	.173
ID_04	.045	1.075	.283	-.003	-.059	.953
ID_05	.047	1.115	.265	-.027	-.640	.522
ID_06	.027	.658	.510	-.005	-.123	.902
ID_07	-.006	-.152	.879	-.035	-.824	.410
	R^2 = .053, $F_{10, 971}$ = 4.664 **p = <.001*****			R^2 = .013, $F_{10, 971}$ = .673, *p* = .751		
Step 3: Baseline factors						
Left-VS	-.063	-1.299	.194	.037	.743	.457
Right-VS	-.012	-.254	.800	-.098	-1.972	**.049***
Age	.056	1.688	.092	.039	1.156	.248
SES	-.008	-.245	.807	-.008	-.237	.812
Gender	-.107	-3.402	**<.001*****	-.014	-.427	.670
ID_01	.085	1.998	**.046***	-.081	-1.872	.061
ID_02	.173	4.052	**<.001*****	-.046	-1.058	.290
ID_03	.049	1.218	.224	-.059	-1.430	.153
ID_04	.032	.746	.456	-.008	-.174	.862
ID_05	.042	.988	.324	-.031	-.717	.475
ID_06	.023	.562	.574	-.007	-.166	.868
ID_07	-.011	-.267	.789	-.041	-.960	.337

Intelligence Estimate	-.024	-.729	.466	.020	.613	.540
Novelty-Seeking Use	.017	.533	.594	.049	1.460	.145
Monthly Alcohol	-.008	-.226	.821	-.019	-.550	.583
Daily Cigarette Use	.064	1.981	.048	-.011	-.350	.727
Lifetime Drug Use	.002	.070	.944	.050	1.458	.145
	R^2 = .058, $F_{5, 966}$ = 1.042 p = .391			R^2 = .018, $F_{5, 966}$ = 1.002, p = .415		
Step 4: Baseline Mood Symptoms						
Left-VS	-.055	-1.144	.252	.048	.977	.329
Right-VS	-.014	-.290	.772	-.102	-2.077	**.038***
Age	.057	1.745	.081	.040	1.190	.234
SES	-.010	-.306	.760	-.011	-.349	.727
Gender	-.097	-3.099	**.002****	-.005	-.154	.877
ID_01	.082	1.953	.051	-.078	-1.814	.070
ID_02	.169	3.980	**<.001*****	-.040	-.915	.360
ID_03	.048	1.210	.227	-.057	-1.400	.162
ID_04	.032	.769	.442	-.008	-.185	.853
ID_05	.044	1.066	.287	-.029	-.679	.497
ID_06	.020	.500	.618	-.010	-.242	.809
ID_07	-.012	-.279	.781	-.035	-.818	.414
Intelligence Estimate	-.026	-.817	.414	.020	.612	.541
Novelty-Seeking	.009	.279	.780	.038	1.154	.249
Monthly Alcohol Use	-.018	-.522	.602	-.028	-.796	.426
Daily Cigarette Use	.064	1.999	**.046***	-.009	-.2269	.788
Lifetime Drug Use	-.011	-.321	.748	.037	1.081	.280
Baseline Depression	.128	3.909	**<.001*****	.054	1.609	.108
Baseline (Hypo)Manic	.062	1.888	.059	.126	3.763	**<.001*****
	R^2 = .082, $F_{2, 964}$ = 12.593 **p = <.001*****			R^2 = .040, $F_{2, 964}$ = 11.03, **p < .001*****		

Note. All reported β estimates are standardized regression coefficients. n = 984
New variables added in each step of model building are bolding to aid the reader.
ID_01: London; ID_02: Nottingham; ID_03: Dublin; ID_04: Berlin; ID_05: Hamburg: ID_06: Mannheim; ID_07: Paris
The VS activation was from the contrast of large-win vs. no-win.
VS, ventral striatum
* p < .05
** p < .01
*** p < .001
Significant findings are bolded to aid the reader.

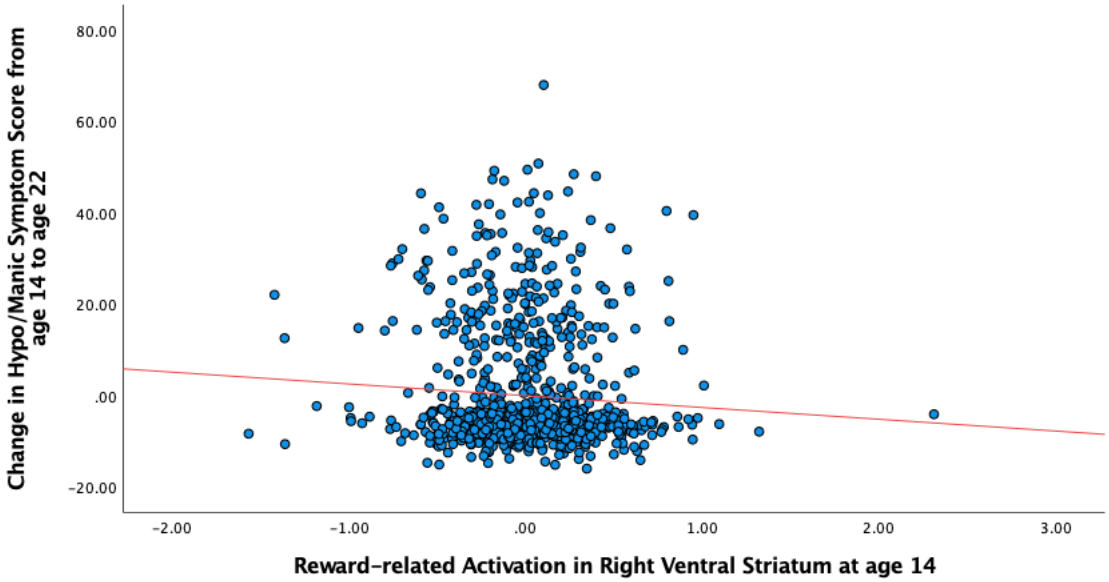
3.7. Prediction of Change in Depressive and (Hypo)Manic Symptoms at Follow-up from Baseline Reward-related Neural Responses

To further substantiate our results, we conducted a multiple regression analysis to investigate whether reward-related activation in the left and right VS at 14 years could significantly predict the change in participants' depression and (hypo)manic symptom scores from age 14 to age 22. The results of the regression indicated that the model was not a significant predictor of the change in depression score from age 14 to age 22, R^2 = 0.04, $F_{2, 981}$ = 784, p = .457 and reward-related activation in the left and right VS at 14 years did not contribute significantly to the model: β = -.038, p = .436 and β = -.002, p = .966, respectively (Table 4). Follow-up hierarchical multiple regressions revealed that including other factors (age, gender, site ID, SES composite score, baseline intelligence estimate, baseline alcohol and drug use, baseline novelty seeking score and baseline mood symptoms at 14 years) did not alter this association (Table 4). Although there was no significant association found between reward-related activation in the bilateral VS at age 14 and change in mood symptom score from age 14 to age 22, adding baseline mood symptoms to the model significantly improved the model's prediction of the change in Depression Symptom Score from age 14 to age 22, R^2 = .416, $F_{2, 964}$ = 322.463, p = <.001. The final model accounted for approximately 41.6% of the variance of the change in Depression Symptom Score from age 14 to age 22. The results showed that site ID, specifically, the Nottingham (02) site, gender, baseline daily cigarette use, and baseline depression symptom scores were associated with change Depression Symptom score from age 14 to age 22 (Table 4). See Figure 5 and Figure 6 in Appendix D for further illustration of these associations.

Similarly, results of the regression indicated that the model was not a significant predictor of the change in (hypo)manic score from age 14 to age 22, R^2 = 0.04, $F_{2, 981}$ = 1.936,

p = .145 and reward-related activation in the left and right VS at 14 years did not contribute significantly to the model, β = .085, *p* = .083 and β = -.095, *p* = .055, respectively (Table 4). However, although reward-related activation in the right and left VS at 14 years did not contribute significantly to the model, reward-related activation in the right VS did approach significance (*p* = .055) and reward-related activation in the left VS was similarly trending towards significance (*p* = .083). Follow-up hierarchical multiple regressions revealed that including other factors (age, gender, site ID, SES composite score, baseline intelligence estimate, baseline alcohol and drug use, baseline novelty seeking score and baseline mood symptoms at 14 years) altered the association between reward-related activation in the right VS, and it became statistically significant, β = -.069, *p* = .038 (Table 4). As shown in Figure 5, increased larger changes in (hypo)manic symptom scores at age 22 were associated with decreased reward-related responses in the right VS at age 14. Further, adding baseline mood symptoms to the model significantly improved the model's prediction of the change in (Hypo)Manic Symptom score from age 14 to age 22, $F_{2, 964} = 579.6$, $p < .001$. The final model accounted for approximately 54.4% of the variance of the change in (Hypo)Manic Symptom Score from age 14 to age 22. The results showed that, in addition to reward-related activation in the right VS at age 14, baseline (Hypo)Manic Symptom Score was associated with the change in (Hypo)Manic Symptom score from age 14 to age 22, β = -.754, *p* <.001 (see Figure 6 in Appendix D for further illustration of this associations).

Figure 5.
Partial Regression Plot of Change in (Hypo)Manic Symptom Score from age 14 to age 22 and Neural Activation in Right Ventral Striatum at age 14.



Reduction of (hypo)manic symptoms at age 22 is predicted by reward-related activation in right ventral striatum at age 14.
Beta estimated for association between activation in right ventral striatum and change in (hypo)manic score is statistically significant.
β = -.069, *p* = .038

Table 4.
Results of Hierarchical Regression Analyses for the Reward-Related Activations of the Bilateral Ventral Striatum at Age 14 and the Change in Depression and (Hypo)Manic Symptom Score from age 14 to Age 22.

	DV Change in Depression Symptoms from age 14 to 22			DV Change in (Hypo)Manic Symptoms from age 14 to 22		
	β	*t*	*p*	β	*t*	*p*
Step 1: Reward-related VS activation at Age 14						
Left-VS	-.038	-.779	.436	.085	1.736	.083
Right-VS	-.002	-.042	.966	-.095	-1.923	.055
	R^2 = .002, $F_{2, 981}$ = .784 p = .457			R^2 = .004, $F_{2, 981}$ = 1.936, p = .145		
Step 2: Demographics						
Left-VS	-.031	-.624	.533	.091	1.823	.069
Right-VS	-.007	-.150	.881	-.096	-1.943	.052
Age	.046	1.380	.168	.023	.692	.489
SES	-.011	-.329	.742	-.028	-.885	.376
Gender	-.039	-1.212	.226	.028	.876	.381
ID_01	.035	.814	.416	-.028	-.653	.514
ID_02	.082	1.895	.058	.029	.664	.507
ID_03	.035	.879	.379	-.028	-.699	.485
ID_04	.037	.870	.385	-.016	-.383	.702
ID_05	.049	1.145	.253	-.018	-.430	.667
ID_06	.008	.202	.840	-.029	-.690	.490
ID_07	-.036	-.855	.393	.019	.444	.657
	R^2 = .017, $F_{10, 971}$ = 1.518 p = .128			R^2 = .010, $F_{10, 971}$ = .588, p = .825		
Step 3: Baseline Factors						
Left-VS	-.031	-.625	.532	.090	1.818	.069
Right-VS	-.007	-.138	.890	-.096	-1.931	.054
Age	.051	1.513	.131	.028	.841	.400
SES	-.007	-.213	.831	-.028	-.874	.383
Gender	-.040	-1.245	.131	.028	.855	.393
ID_01	.035	.819	.413	-.018	-.424	.671
ID_02	.083	1.915	.056	.038	.867	.386
ID_03	.026	.635	.526	-.022	-.529	.597
ID_04	.031	.727	.467	-.011	-.253	.800
ID_05	.047	1.097	.273	-.016	-.361	.718
ID_06	.009	.214	.831	-.021	-.493	.622
ID_07	-.035	-.813	.416	.027	.625	.532
Intelligence Estimate	-.037	-1.117	.264	.021	.630	.529

Novelty-Seeking Use	-.010	-.299	.765	-.026	-.761	.447
Monthly Alcohol	-.050	-1.413	.158	-.049	-1.385	.166
Daily Cigarette Use	.040	1.222	.222	.016	.473	.636
Lifetime Drug Use	-.047	-1.363	.173	-.031	-.890	.374
	R^2 = .025, $F_{5, 966}$ = 1.611 p = .154			R^2 = .016, $F_{5, 966}$ = 1.211, p = .302		
Step 4: Baseline Mood Symptoms						
Left-VS	-.044	-1.144	.253	.033	.977	.329
Right-VS	-.011	-.290	.772	-.069	-2.077	**.038***
Age	.045	1.745	.081	.027	1.190	.234
SES	-.008	-.306	.760	-.008	-.349	.727
Gender	-.077	-3.099	**.002***	-.003	-.154	.877
ID_01	.066	1.953	.051	-.053	-1.814	.070
ID_02	.135	3.980	**<.001****	-.027	-.915	.360
ID_03	.038	1.210	.227	-.039	-1.400	.162
ID_04	.026	.769	.442	-.005	-.185	.853
ID_05	.035	1.066	.287	-.020	-.679	.497
ID_06	.016	.500	.618	-.007	-.242	.809
ID_07	-.009	-.279	.781	-.024	-.818	.414
Intelligence Estimate	-.021	-.817	.414	.014	.612	.541
Novelty-Seeking	.007	.279	.780	.026	1.154	.249
Monthly Alcohol Use	-.014	-.522	.602	-.019	-.796	.426
Daily Cigarette Use	.051	1.999	**.046***	-.006	-.269	.788
Lifetime Drug Use	-.009	-.321	.748	.025	1.081	.280
Baseline Depression	.049	1.888	**<.001****	.037	1.609	.108
Baseline (Hypo)Manic	-.646	-24.796	.059	-.754	-33.032	**<.001****
	R^2 = .416, $F_{2, 964}$ = 322.463 ***p* = <.001****			R^2 = .553, $F_{2, 964}$ = 579.6, ***p* < .001****		

Note. All reported β estimates are standardized regression coefficients. n = 984
New variables added in each step of model building are bolding to aid the reader.
ID_01: London; ID_02: Nottingham; ID_03: Dublin; ID_04: Berlin; ID_05: Hamburg: ID_06: Mannheim; ID_07: Paris
The VS activation was from the contrast of large-win vs. no-win.
VS, ventral striatum
* p < .05
** p < .001
Significant findings are bolded to aid the reader.

3.8. Prediction of Depressive and (Hypo)Manic Symptoms at Follow-up from Baseline Reward-related Neural Responses Excluding Participants Taking Psychotropic Medication at Baseline

To explore whether the use of psychotropic medication was influencing the above findings, we performed the above analyses on a subsample of participants by removing participants who had reported taking psychotropic medication at age 14 years (n = 968). This, similarly, did not alter the relationship between the activations in the bilateral VS at age 14 and the depression and (hypo)manic symptom score at age 22: Depression Symptom Score: R^2 = .008, $F_{2, 965}$ = 3.736, p = .024; (Hypo)Manic Symptom Score: R^2 = .005, $F_{2, 965}$ = 2.217, p = .109 (See Table 2 in Appendix E for results of multiple regression analyses).

3.9. Association Between Depressive and (Hypo)Manic Symptoms at Follow-up (age 22)

To explore whether the confluence of depressive and (hypo)manic symptoms was influencing the above findings, a Pearson correlation coefficient was computed to assess the linear relationship between depressive and (hypo)manic symptoms at follow-up (age 22). There was a positive correlation between the two variables, $r(1078) = .246$, $p < .001$.

4. Discussion

This is the first study to examine neural reward function as a predictor of bipolar spectrum disorder (BSD) symptoms using a longitudinal approach in a community sample of adolescents followed from age 14 to age 22. By elucidating the mechanisms that may contribute to BSD psychopathology, we sought to contribute to a broader understanding of the pathophysiology of BSD. The current study's research questions and hypotheses, and planned analyses were preregistered on Open Science Framework (https://osf.io/8bue5) prior to any data being downloaded or analysed. We utilised a monetary incentive task (Knutson et al., 2001) to investigate whether neural responses in the ventral striatum (VS) during anticipation of rewards were associated with depressive and hypo(manic) symptoms at baseline. We also aimed to examine this relationship longitudinally to determine whether these reward-related responses predicted intensification of mood symptoms at eight-year follow-up.

No significant association was found between reward-related neural responses and depressive or (hypo)manic symptoms at baseline, contrary to our predictions (Hypothesis 1 and Hypothesis 2). Analysis to explore the impact of demographic and clinical variables on this relationship found that none of these significantly altered the relationship between neural responses to reward and mood symptoms. In contrast, a significant association was found between baseline reward related responses in the VS and mood symptoms at follow-up. Our findings suggest that neural responses in the VS during anticipation of rewards at age 14 predicted mood symptom load at age 22, despite the lack of association between reward-related responses and mood symptoms at age 14. Thus, it may be that striatal activation represents a putative biomarker for increased risk to the development and intensification of mood symptoms. However, in contrast to our predictions (Hypothesis 3), a significant

association was only observed for (hypo)manic symptoms and higher baseline neural responses to reward were found to predict a reduction in (hypo)manic symptoms at follow-up. Below, we discuss each of these findings in turn, and their implications for understanding the pathophysiology of BSD.

4.1. Association of Depressive and (Hypo)Manic Symptoms with Baseline Reward Neural Response (Hypothesis 1 and Hypothesis 2)

Although functional magnetic resonance imaging (fMRI) studies have provided some compelling albeit nuanced support for the reward hypersensitivity model of BSD (see Nusslock & Alloy 2017 for a review), as described above, there are conflicting findings of increased, reduced, and no differences in VS reward-related activation between BSD and control groups. As previously described, these discrepant findings may be due to a number of factors, including the impact of BSD chronicity and associated secondary confounds, medicated samples, and limited exploration of the impact of (hypo)manic and depressive symptoms simultaneously (Bart et al., 2021). We sought to shed light on previously mixed findings, with a preclinical population to minimise the impact of BSD chronicity, psychotropic medication and by examining the relationship between depressive and (hypo)manic symptoms and reward processing simultaneously.

Here we confirm that the VS, a key component of the reward circuitry shown to be involved in anticipating rewards (Diekhof et al., 2012), is activated (indicated by an elevated BOLD signal) during anticipation of rewards in this sample of adolescents. However, we were unable to confirm a relationship between altered VS engagement in anticipation of reward and BSD symptoms in our cross-sectional analyses. To answer our cross-sectional hypotheses, we tested whether a) Depressive symptoms were associated with a blunted striatal response

(H1a) and (hypo)manic symptoms were associated with elevated striatal responses during reward anticipation (H1b), and b) Individuals who were at risk for BSDs (experience both elevated depressive and (hypo)manic symptoms, showed elevated striatal responses during reward anticipation (H2). Contrary to our cross-sectional hypotheses, reward-related activations in the VS were not associated with depressive (Hypothesis 1a) and (hypo)manic symptoms (Hypothesis 1b) measured at the same time point (age 14). Similarly, contrary to our Hypothesis 2, risk for BSD at age 14 (the interaction between depressive and (hypo)manic symptoms) was not associated with reward-related activation in the VS at age 14.

The absence of a relationship between reward-related activation and concurrently measured mood symptoms may indicate that elevated anticipatory reward activation in the VS might not represent a risk marker for BSD that lies on a continuum which extends through this non-clinical sample. This is in line with previous studies who have noted a similar absence of relationship (Berghorst et al., 2016; Bermpohl et al., 2010; Chase et al., 2013; Dutra et al., 2015; Kollmann et al., 2017; Linke et al., 2012; Yip et al., 2015). However, this is in contrast to the to the Reward Hypersensitivity model of BSD which argues that a hypersensitivity to goal- and reward-relevant cues underlies the risk for BSD symptoms, and particularly (hypo)manic symptoms (Alloy & Abramson, 2010; Alloy, Bender, et al., 2009; Alloy et al., 2015; Johnson, 2005b; Johnson et al., 2012; Nusslock et al., 2014; Urošević et al., 2008). Furthermore, this is in contrast to the argument that a propensity for enhanced reward and approach-related neural activation is a central mechanism underlying the hypersensitivity to goal- and reward-relevant cues, and which consequently confers vulnerability to developing (hypo)manic symptoms in the presence of reward-relevant signals (Johnson, 2005b; Johnson et al., 2012; Nusslock & Alloy, 2017).

Conversely, it may be that enhanced anticipatory reward activation in the VS does represent a risk marker for BSD as proposed by the Reward Hypersensitivity model of BSD, however, we were unable to detect this in a non-clinical sample. The current study utilised a pre-clinical sample and timepoint that typically precedes the peak onset for BSD (Jones & Tarrier, 2005), to minimize the impact of BSD chronicity and associated secondary confounds. However, the use of a pre-clinical sample likely restricted the range of BSD symptoms and may have consequently reduced the power to detect associations between BSD symptoms and reward-related neural activation in the VS. Future research could clarify this through the examination of the relationship between mood symptoms and reward-related activation in the VS using additional timepoints, for example, middle adolescence and late adolescence as the range of BSD symptoms reported by participants may expand, increasing the power to detect relationships between these symptoms and reward-related activation. Moreover, future research could further substantiate this hypothesis by stratifying participants according to level of clinical severity of symptoms and examining differences in reward-related activation across these groups. We would argue that this approach would identify a relationship between reward-related activation and mood symptoms such that enhanced reward-related neural responses will be associated with an increased symptom load.

Furthermore, research has shown that normative adolescence is characterised by emotional instability and reward hypersensitivity (Urošević et al., 2012; Urošević et al., 2016). Moreover, the experience of (hypo)manic symptoms seems to be common during adolescence (Stringaris et al., 2014); prior research has suggested incidence rates of (hypo)manic symptoms to be 1720 in 100,000, which is higher than previously estimated (Tijssen et al., 2010). However, these (hypo)manic symptoms are generally transient and may represent a developmental stage (Casey et al., 2010). Therefore, adolescence represents a

developmental period that is particularly noisy in relation to psychopathological symptoms and reward sensitivity, which may have limited our ability to detect a relationship between BSD symptoms and reward-related neural responses. Furthermore, research has suggested that adolescence is characterised by enhanced emotional reactivity which may be attributable to a disparity between the development trajectories of limbic subcortical regions and prefrontal cortical regions (Casey et al., 2010). This imbalance model proposes that subcortical regions crucial to emotional processing develop earlier than cortical regions necessary for emotional regulation, contributing to enhanced sensitivity to reward-relevant cues (Casey et al., 2008; Somerville et al., 2010). In support of the imbalance model, research has observed exaggerated responses to affective cues in subcortical regions in adolescents relative to children or adults (Ernst et al., 2005; Guyer et al., 2009; Guyer et al., 2008; Monk et al., 2003; Williams et al., 2006). Therefore, a general tendency towards exaggerated response magnitudes in subcortical areas may have further limited our ability to detect any relationship between mood symptoms and reward-related striatal activation. However, these exaggerated responses may result in an increased need for top-control processes that recruit prefrontal regions (Casey et al., 2010). Therefore, it may be that the association with mood symptoms might be better captured by exploring top-down control processes that may be modulating VS activity, for example by exploring the connectivity between VS and the ventral prefrontal cortex.

Additionally, the emotional dysregulation that is characteristic of this developmental period may compromise the validity of measures such as the Developmental and Wellbeing Assessment Interview (DAWBA). For example, individuals at age 14 may report emotional instability that reflects normative levels of emotion dysregulation. Consequently, the DAWBA, and particularly the (hypo)manic items in the DAWBA may capture normative phenomena

and fail to discriminate between these phenomena and indications of psychopathology. Future research could investigate this further by investigating the relationship between reward-related activation and mood symptoms at additional timepoints, such as middle and late adolescence, and young adulthood. As individuals move through adolescence, the heightened emotional dysregulation characteristic of early adolescence may subside. Consequently, the measurement validity of the DAWBA may be enhanced. Validity of the DAWBA could further be enhanced in future research by the inclusion of other relevant measures in analyses such as the Young Mania Rating Scale (Young et al., 1978) or the Adolescent Depression Rating Scale (Revah-Levy et al., 2007). Furthermore, future research could explore whether there are systematic differences between parent and self-report versions of the DAWBA and could examine whether there is a relationship between reward-related activation and parent-reported mood symptoms. In accordance with the above-mentioned arguments, this may facilitate the detection of a relationship between reward-related activation and mood symptoms, such that higher incidences of symptoms will be associated with elevated reward-related neural activation.

4.2. Prediction of Depressive and (Hypo)Manic Symptoms at Follow-up from Baseline Reward Response (Hypothesis 3)

As previously described, although there is evidence that BSD is associated with reward hypersensitivity in the fronto-striatal reward circuit (Bart et al., 2021) and behavioural research has implicated reward hypersensitivity as a trait vulnerability to BSD (Nusslock & Alloy, 2017), neuroimaging findings regarding neural reward hypersensitivity as a trait vulnerability to BSD is limited (Bart et al., 2021). Hence, we sought to explore whether reward-related striatal activation at baseline predicted mood symptom load at follow-up. To answer

our longitudinal hypotheses, we tested whether reward-related neural responses in the VS at baseline (age 14) were associated with the change in mood symptom load from baseline (age 14) to follow-up (age 22). Despite the lack of association between reward-related responses and mood symptoms at age 14, we were able to confirm that baseline reward-related striatal activation predicted mood symptom load at baseline. However, the observed association occurred in the reverse direction than was predicted. Participants with higher neural responses to anticipation of large monetary gains (indicated by an elevated BOLD signal in the contrast of large versus no reward) at baseline, had lower levels of both depressive and (hypo)manic symptoms at follow-up, however, only the association between reward-related activation and (hypo)manic symptoms was statistically significant.

The finding that greater baseline reward-related activations predicted lower levels of depression symptoms at follow-up does not support the argument made by the Reward Hypersensitivity model of BSD that a hypersensitivity to goal-and reward-relevant cues underlies the risk for both (hypo)manic and depressive symptoms (Depue et al., 1987; Urošević et al., 2008). However, it has recently been proposed that reward hypersensitivity may be more strongly related to vulnerability for (hypo)manic symptoms rather than bipolar depressive symptoms and that different aetiological mechanisms may underlie bipolar depression (Nusslock & Alloy, 2017). For example, it may be that the same blunted reward profile that has been observed in unipolar depression, may similarly underlie risk to develop bipolar depression (Alloy et al., 2016). The observation that greater baseline reward-related activations predicted lower levels of depression symptoms at follow-up may be understood within this multifinality perspective and in particular in relation to anhedonia. Anhedonia, a key diagnostic criterion of major depression, is described as a loss of responding to rewarding stimuli and a loss of pleasure in activities previously considered enjoyable (Arjmand et al.,

2018). Several lines of evidence have consistently shown that individuals with blunted reward sensitivity are vulnerable to developing unipolar depression due to a diminished capacity to seek out and react to rewards (Alloy et al., 2016). For example, decreased approach motivation and positive affect have been concurrently and prospectively linked to unipolar depression onset in adults (Nusslock & Alloy, 2017). Furthermore, a recent meta-analysis identified a significant association between unipolar depression and reduced neural activation in the VS during the anticipation and receipt of monetary and other rewards (Zhang et al., 2013). Therefore, it may be that the elevated responses observed in the VS at baseline in the current study served as a protective factor against development of depression at follow-up resulting in a lower incidence of depressive symptoms. In support of this argument, blunted neural responses in the VS during the anticipation of rewards was found to predict increases in depressive symptoms in a two-year follow-up (Alloy et al., 2016). Similarly, blunted reward responses in the VS have been described in adolescents at risk for depression (Gotlib et al., 2010) and have been found to predict increases in depressive symptoms (Morgan et al., 2013).

The finding that increased reward-related activation at baseline predicted decreased (hypo)manic symptoms at follow-up is surprising, given that reviews of the literature have suggested that reward hypersensitivity in the fronto-striatal circuit is implicated is BSD (Bart et al., 2021; Nusslock & Alloy, 2017). However, as noted in the introduction, findings regarding the VS have been mixed; some studies have reported increased activation (Dutra et al., 2015; Nusslock et al., 2012; Singh et al., 2013), others have reported decreased activation (Abler et al., 2008; Johnson et al., 2019), and still others have reported no differences between BSD and healthy controls (Bermpohl et al., 2010). We argued that these conflicting findings may have been due to subthreshold depressive and (hypo)manic symptoms influencing reward

processing, despite individuals being classified as being in distinct, disparate episodes (Bart et al., 2021). The current study, therefore, sought to examine the independent relationships between 1) depressive and 2) (hypo)manic symptoms and reward processing, simultaneously. There may be several explanations for our finding that increased reward-related activation at baseline predicted lower levels of (hypo)manic symptoms at follow-up.

Firstly, one potential explanation for the association between activation at baseline and (hypo)manic symptoms at follow-up observed in the current study can be found by examining addiction literature. Altered reward processing, particularly reward sensitivity, is associated with problematic substance use and the onset and course of substance use disorders (Alloy, Bender, et al., 2009; Bart et al., 2021; Dawe et al., 2004; Dawe & Loxton, 2004). One theory put forth to explain these findings is the Reward Deficiency Model of addiction, which posits that addictive behaviours represent an individual's compensatory efforts to offset a blunted reward profile characterised by a lack of recruitment of the reward circuit and reduced capacity to experience pleasure from rewards (Blum et al., 2000; Bowirrat & Oscar-Berman, 2005; Volkow et al., 2003). In line with this theory, blunted responses in the VS during anticipation of rewards have been observed in substance (Schouw et al., 2013) and alcohol abuse (Beck et al., 2009; Schouw, 2013). Similarly, more recent studies examining reward processing in individuals with BSD have observed blunted responses in the VS during anticipation of rewards using the MID task (Johnson et al., 2019; Schreiter et al., 2016) and unmedicated individuals (Yip et al., 2015). Blunted responses to reward may contribute to increased incidences of reward-seeking behaviour as individuals try to counteract this blunted reward profile (Robbins & Everitt, 1999). Increased reward-seeking behaviour could manifest as increased impulsivity and pursuit of rewarding activities without attention to risks, which may confer risk to the subsequent development of (hypo)manic symptoms and onset of BSD

(Johnson et al., 2019). Viewed through this lens, elevated reward-related responses in the VS during anticipation of rewards at baseline may confer a degree of protection against increased reward-seeking behaviour and consequently, lead to lower (hypo)manic symptoms at follow-up. This argument would be substantiated by future research that includes a measure of impulsivity or sensation-seeking at follow-up.

Secondly, the finding that enhanced reward-related activation at baseline predicted lower (hypo)manic symptoms at follow-up, may reflect an inability to dissociate the separate effects of (hypo)manic symptoms from the confluence of depressive and (hypo)manic symptoms in the current study. We had previously hypothesised that (hypo)manic and depressive symptoms may have opposing or independent relationships with reward processing, which may have contributed to the discrepancy in findings in the current literature on the relationship between reward processing and mood symptoms (Alloy & Nusslock, 2019). This may also be the case in the current study. However, analyses showed that depressive and (hypo)manic symptoms were only weakly correlated at baseline and follow-up. Thus, it does not appear as though depressive and (hypo)manic symptom dimensions were too collinear to decouple in the current study. This suggests that the association between reward-related activation at baseline and (hypo)manic symptoms at follow-up is not attributable to the confluence of depressive and (hypo)manic symptoms.

Finally, it may be that individuals who displayed elevated reward-related activation at baseline were at increased risk for developing BSD and as such came to clinical attention and engaged in help-seeking behaviour. As a result of this, these individuals may have been in receipt of psychotropic medication or psychotherapeutic interventions at follow-up which may have contributed to the decrease in mood symptom load. Although, information regarding psychotropic medication use and other help-seeking behaviour was absent at

follow-up, excluding individuals who were in receipt of psychotropic medication at baseline did not alter the observed association. Thus, it does not appear as though the use of psychotropic medication influenced the findings in the current study. However, this argument would be substantiated by future research that examines the impact of psychotropic medication use at follow-up on the association between baseline reward-related neural activation and mood symptoms at follow-up.

4.3. Associations Between Reward-related Responses, Mood Symptoms and Other Variables

Our study identified an association between study site and level of activation in bilateral VS at baseline, and mood symptom scores at follow-up. Acquiring and sharing large amounts of neuroimaging data is crucial in furthering our understanding of the underlying mechanisms of psychopathology and applying this understanding in clinical practice. However, multi-site studies are often necessary to collect such large amounts of data and significant challenges are raised in multisite datasets, namely site differences that are attributable to engineering bias and sampling bias (Yamashita et al., 2019). Engineering bias refers to differences in MRI scanner type and imaging protocol parameters such as field strength whereas sampling bias refers to differences in participants across sites (Yamashita et al., 2019). To control for such site differences, it is recommended to include a site factor in analysis models (Turner et al., 2013). While the imaging protocols in the current study were developed to be compatible with MRI scanners of all manufacturers, all sites utilised standardised methods for acquisition of neuroimaging data and behavioural/neuropsychological assessment and quality control procedures were regularly implemented across all sites, site specific variation could not be avoided (Schumann et al., 2010). However, significant associations between reward-related neural responses at age 14

and mood symptoms at age 22 were not affected by the inclusion of site ID in the regression model. This supports the argument that these effects are robust to site variation.

The current study identified an association between baseline mood symptoms and mood symptoms at follow-up, such that higher levels of depressive and (hypo)manic symptoms at baseline were associated with higher levels of depressive and (hypo)manic symptoms at follow-up, respectively. This is in line with clinical and research evidence that those who experience symptoms at a younger age are at increased risk for intensification of symptoms at later stages (Bertha & Balázs, 2013; Treuer & Tohen, 2010). It may be that adolescents who experience subthreshold symptoms are at increased risk for poorer quality of life, increased distress and substantial functional impairment which may contribute to an escalation in symptoms (Bertha & Balázs, 2013). Furthermore, adolescents who experience subthreshold mood symptoms have also been shown to display higher levels of psychosocial dysfunction and substance use disorders (Lewinsohn et al., 2000). This suggests these adolescents may experience reduced access to protective factors and positive sources of support, such as their peer group. Additionally, these adolescents may rely on more maladaptive emotion regulation strategies such as substances or alcohol which can exacerbate their mood difficulties.

Relatedly, we also identified an association between baseline daily cigarette use and depressive symptoms at follow-up such that higher levels of daily cigarette use at baseline was associated with higher levels of depression at follow-up. This is in line with prior research that has also found that smoking predicts increasing levels of depressive symptoms over time (Brown et al., 1996; Chaiton et al., 2009; Lechner et al., 2017; Wang et al., 1996; Windle & Windle, 2001). This association may be due to the impact of persistent smoking on brain biochemistry, particularly dopaminergic transmission, which may increase vulnerability to

developing depression (Windle & Windle, 2001). An alternative explanation may relate to an emotion-regulation model in which adolescents who are more likely to engage in maladaptive emotion regulation strategies such as smoking which provide transitory relief but not long-term mental health benefits, may consequently fail to develop other more adaptive strategies such as problem-solving to manage affective triggers (Leventhal & Zvolensky, 2015). This may contribute to a higher incidence of mood symptoms.

Finally, the current study identified an association between gender and depressive symptoms such that females reported higher levels of depression at follow-up. This theme of female preponderance of depression in adolescence and adulthood is one of the most replicated findings in epidemiology (Dyer & Wade, 2012; Kessler et al., 1993; Nolen-Hoeksema & Hilt, 2009). However, the mechanisms underlying the high female to male ratio in the prevalence of depression still remain unclear (Piccinelli & Wilkinson, 2000). A detailed discussion of the potential mechanisms underlying the female preponderance in depression is beyond the scope of this paper, however, in brief, the association between gender and depressive symptoms at follow-up may reflect the interaction of various biopsychosocial factors including gender socialisation (Cyranowski et al., 2000), gonadal hormone changes (McGrath et al., 1990), higher rates of physical and sexual abuse (Weiss et al., 1999), and increased reactivity to stressful events (Shih et al., 2006).

4.4. Strengths and Limitations

This is the first study to examine the relationship between reward processing and (hypo)manic and depressive symptoms longitudinally in a large community-based sample of adolescents. Further, we examined subthreshold (hypo)manic and depressive symptoms, and their relationship with reward-related neural responses simultaneously, rather than

classifying participants as being in distinct and disparate episodes. Moreover, we used a preclinical population to minimise the potential impact of psychotropic on dopaminergic transmission in the fronto-striatal circuit, and we additionally controlled for this in our cross-sectional analyses. However, as this information was not collected at follow-up, we were unable to control for the potential impact of psychotropic medication on follow-up mood symptoms at age 22. We were similarly unable to control for the potential influence of help-seeking and engaging in psychotherapeutic intervention on mood symptoms at follow-up. Secondly, although we chose an adolescent population to minimise the impact of disorder chronicity and associated confounds, adolescence is also a time of rapid and drastic changes within the brain. As normative reward processing undergoes developmental change itself (Bart et al., 2021; Kollmann et al., 2017), we cannot be certain that findings from an adolescent sample will be generalisable to adults.

Thirdly, we selected the contrast of large reward versus no reward in line with prior research investigating the neural mechanisms underlying anticipation of rewards (Berghorst et al., 2016; Dutra et al., 2015; Johnson et al., 2019; Kollmann et al., 2017; Schreiter et al., 2016; Yip et al., 2015). However, it may be that this contrast was masking subtle differences in reward sensitivity and their relationship with mood symptoms. For example, a previous study did not identify significant group differences in the anticipation of large versus no rewards between participants with BSD and healthy controls (Abler et al., 2008). However, this study noted that the difference in the signal time courses for high and not rewarded stimuli were significantly reduced in participants with BSD, thus all stimuli were viewed as equally salient (Abler et al., 2008). Therefore, it may be that reward processing is dysregulated is individuals with elevated mood symptoms in the current study, but the

pattern is too subtle to be detected when contrasting the anticipation of large rewards versus no rewards.

Finally, although our power analysis suggests that an implied power of was achieved with our sample size, the standardised beta estimates were small, and the total variation in mood symptom scores at follow-up accounted for by our models was similarly small. Given that many factors are likely to contribute to the development of mood symptoms in young adulthood, it is perhaps unsurprising to observe effect sizes of the magnitude we observed due to a single-factor, such as reward-related neural responses. However, we would argue that understanding the neurophysiological mechanisms underlying reward processing is particularly important in understanding psychopathology. Reward processing is crucial to adaptive decision-making; neural processing of anticipation of rewards takes place immediately prior to a choice and is perfectly timed so as to influence decision making (Knutson & Greer, 2008; Trepel et al., 2005). Thus, reward processing is evident in the thousands of decisions made every day. Aberrations within the reward system have detrimental effects on behaviour and compromise an individual's ability to choose between different courses of action (Balodis & Potenza, 2015; Diekhof et al., 2008). This may have important economic consequences; for example, individuals do not invest in a pension as their decision-making has been influenced by disruptions in reward processing. Thus, at the population level, understanding the specific choice situations in which reward processing affects decision-making may be useful for policymakers and on a broader societal level.

4.5. Conclusions

In summary, our findings provided some evidence for a relationship between aberrant reward processing and BSD symptoms. We did not find an association between reward-

related activation during anticipation of rewards at age 14 and depressive and (hypo)manic symptoms at age 14. However, in spite of this absence of an association, we observed an association between reward-related striatal activation at age 14 and changes in mood symptom score at age 22. Our findings suggest that individuals with enhanced sensitivity to anticipation of rewards at age 14 had lower (hypo)manic symptoms at age 22, and further tended to exhibit lower depressive symptoms at age 22, although this finding did not reach statistical significance.

4.6. Implications for Research and Clinical Practice

A number of factors, such as the absence of a well-established animal model of the salient features of BSD in one model, the multifactorial nature of the disorder, the limited number of longitudinal studies with large sample sizes, and the limited number of prognostic studies, have compromised our understanding of the underlying biological mechanisms of the BSD presentation (Arjmand et al., 2018). However, neuroimaging studies offer the opportunity to illuminate the neural mechanisms underlying pathophysiology of BSD. Thus, whilst the findings of the current study may not currently offer implications that can be applied directly in clinical practice, our findings contribute to the existing literature examining the mechanisms that underlie BSD psychopathology. Our longitudinal findings show that reward-related responses in early adolescence are predictive of future mood symptoms. Thus, as previously stated, our findings may suggest that vulnerability to BSD might not be conferred by hypersensitivity to reward, but rather, by a need to compensate for intrinsic reward hyposensitivity by seeking out higher levels of reward in situations of higher risk. Therefore, the results of this study could inform hypotheses for future research to more thoroughly explore whether enhanced reward-related activation represents a protective

factor against later development of BSD symptoms. Additionally, connectivity studies examining the functional connectivity between the VS and other integral regions in the fronto-striatal circuit such as the prefrontal cortex may provide further insight into the neural mechanisms of reward processing and their role in BSD psychopathology. Such investigations should also be conducted in samples with genetic risk conferred by a family member with BSD. This may subsequently facilitate the identification of potential endophenotypes of BSD. Such endophenotypes may be correlated with externally valid behaviours and symptoms profiles to provide informative and reliable markers of symptoms underlying BSD (Johnson et al., 2019). These biomarkers may be used to identify individuals who are particularly vulnerable to developing BSD in the future and may ultimately provide targets to guide early intervention for such individuals (Büchel et al., 2017). Furthermore, such biomarkers may provide more precise targets for therapeutic intervention in BSD (Nusslock & Alloy, 2017).

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Part 3: Critical Appraisal

1. Introduction

This critical appraisal discusses key reflections that arose on completing the current research. These include researcher influences and positionality, the challenges of neuroimaging and psychological research, and the value of understanding the neurobiological mechanisms underlying psychopathology.

1.1. Influences on Current Research

The clinical and research experience I gained prior to starting training was varied. Following the completion of my BA in Neuroscience at Trinity College Dublin, I was drawn to the more clinical applications of neuroscience and understanding the impact of brain processes on behaviour, which led me down the road to clinical psychology. On my journey towards clinical training, I completed an MRes in Developmental Neuroscience and Psychopathology at the Anna Freud Centre, University College London. It is whilst completing this degree that I was introduced to multiple perspectives of psychopathology and further came to appreciate the value of integrating these perspectives in both research and clinical practice. During this time, I completed a yearlong placement in a clinical neuroimaging lab, which conducted studies using a variety of neuroimaging techniques to investigate the neurobiological mechanisms underlying autism spectrum disorders. I was captivated by the research process and was particularly excited to be using innovative techniques such as functional magnetic resonance imaging (fMRI) and eye-tracking to illuminate the relationship between brain and behaviour. I was particularly interested in the studies that used these novel techniques to understand the mechanisms underlying the efficacy of clinical interventions (Venkataraman et al., 2016). This further highlighted that importance of integrating multiple perspectives in the pursuit of understanding psychopathology and

alleviating psychological distress. Moreover, this additionally motivated me to pursue a neuroimaging project whilst on clinical training to further develop my skills and understanding in conducting clinical neuroimaging research.

During my time on clinical training, I have also taken part in other research projects, including my service-related project, which highlighted the value of service-level research to generate practice-based evidence to inform and improve clinical practice. I also completed a leadership placement at the Foundation for People with Learning Disabilities, which primarily utilised an action research approach to inform and influence the development of evidence-based practice and influence policy at a national and local governmental level. Thus, I have experienced a wide range of the ways in which research can be employed in clinical psychology. As someone who has an interest and passion for clinical neuroscience which is largely based in a scientific realism approach (Yan & Hricko, 2017) and has been critiqued for being too reductionistic (Krakauer et al., 2017), and who has similarly been drawn to the ideas of social constructionism whilst on my time on training (Gergen, 1992), I have at times felt torn between these two approaches. However, my experiences throughout this project have given me the opportunity to reflect on this conflict and have further led me cast a more critical eye on neuroimaging research and research in the field of clinical psychology in general.

1.2. Challenges in Producing Transparent and Reproducible Neuroimaging Research

Since its emergence in the early 1990s, neuroimaging, and in particular fMRI, has been used extensively to further our understanding of the link between brain and behaviour and the neural basis of psychopathology (Poldrack et al., 2017; Schleim & Roiser, 2009; Specht, 2020). The past two decades have produced substantial insights into the functioning of the human brain and have enabled scientists to bridge the gap between animal and lesion studies

(Schleim & Roiser, 2009). However, whilst these advances afford us the opportunity to gain important insights about human behaviour, they are not without their limitations (Gorgolewski & Poldrack, 2016). Issues have been recently highlighted such as a lack of reproducibility, challenges in interpreting findings, and the applicability of findings to groups versus individuals (Flournoy et al., 2020). It is important to note that several of these issues are not specific to the field of clinical neuroscience but have plagued the field of psychological research more generally (Flournoy et al., 2020; Gelman & Loken, 2014; Ioannidis, 2005; Simmons et al., 2016). However, they require careful and ongoing attention to enable researchers in the field of clinical neuroscience to be able to draw strong, defensible and reliable inferences from neuroimaging data that can subsequently be applied to clinical practice (Flournoy et al., 2020). As such, these were important to reflect on as I progressed through my research project.

1.2.1. The Replication Crisis and its Consequences

In keeping with almost every other field of psychology and medicine, the field of neuroimaging has undergone a crisis of replicability; recent studies have suggested that the reliability of fMRI studies is severely limited (Poldrack et al., 2017; Specht, 2020). The cost of conducting fMRI studies alongside potent pressure from the majority of top journals to publish novel findings has contributed to a limited number of direct replications (Gorgolewski & Poldrack, 2016). Further, in cases where replications have been attempted, the replicability of neuroimaging findings has been extremely low (Poldrack et al., 2017). This may be due to a number of factors. Firstly, fMRI data typically contains a time-series of hundreds of 3D images, which represent an indirect measure of neuronal activity across the brain over a period of time, with each image acquired every few seconds (Schleim & Roiser, 2009). These

images are divided into thousands of voxels, which represent the spatial unit of measurement of fMRI. These images must be pre-processed before analysis, in other words, they must be manipulated in a range of different ways including realignment, co-registration, normalisation and smoothing. Therefore, a typical fMRI analysis pipeline contains numerous steps and operations, each with decisions to be made about parameters and methods, resulting in a "garden of forking paths" (Gelman & Loken, 2013) and generating the potential for a perfect storm of irreproducible results (Poldrack et al., 2017). These 'researcher degrees of freedom', as they are known, can result in substantially higher risk of Type I error, even in the absence of P-hacking (Gelman & Loken, 2014; Poldrack et al., 2017; Simmons et al., 2016). Furthermore, researchers tend to report their findings through a clear and simple narrative, and often engage in HARKing, a process in which hypothesising is conducted after results are known, which often obfuscates the exploratory process and data-driven choices that have led to the finding (Kerr, 1998). Issues relating to replicability and researcher degrees of freedom have prompted the neuroimaging research community to respond with several initiatives such as ReproNim (Kennedy et al., 2019). Similarly, the Organisation of Human Brain Mapping announced several best practice and data sharing initiatives (https://www.ohbmbrainmappingblog.com/). One recommendation is for researchers to pre-register their methods and analysis plans, including details of planned sample size, specific analytic tools and software to be used, and hypotheses and predicted outcomes (Flournoy et al., 2020; Gorgolewski & Poldrack, 2016). The Open Science Framework (Foster & Deardorff, 2017) is a well-established platform for pre-registration and is the platform that I used to publish a pre-registration outlining my method and analytic plans for my research project. I found the process of completing a pre-registration incredibly helpful as it helped me to think through and formulate my hypotheses before seeing the data. It has also been

important to pre-register my research plan, particularly in light of the null effects and findings occurring in the reverse direction than was predicted in my empirical project.

Furthermore, a substantial amount of data is collected in neuroimaging research which often requires thousands of statistical comparisons (Kriegeskorte et al., 2009). The approach most often used involves mass univariate testing in which a separate hypothesis test is performed for each voxel (Poldrack et al., 2017). This significantly increases the risk of false positives, as demonstrated by the infamous 'dead salmon' study in which neural activation was detected in the brain of a dead salmon (Bennett, Miller, et al., 2009). This activation disappeared once correction for multiple comparisons was applied, highlighting the necessity of correcting for multiple comparisons. Well-established methods for correcting for multiple comparisons exist, however, there is ongoing debate about whether these methods are too permissive, increasing the risk of type I error (Wager et al., 2007), whereas other researchers have argued that current methods are too stringent and increase the risk of interesting effects going undetected (Lieberman & Cunningham, 2009). The method of correction for multiple comparison represents an important decision that must be made. Unfortunately, some have argued that researchers apply principled correction approaches inconsistently and do not document their decision-making process (Bennett, Wolford, et al., 2009; Poldrack et al., 2017). As stated above, this can have serious implications for the interpretation and reproducibility of findings. One approach to minimise the impact of multiple comparisons is to employ a region of interest (ROI) approach in which only a limited number of voxels within a specified region are analysed, therefore reducing the number of comparisons (Flournoy et al., 2020; Poldrack, 2007), which is the method we employed in the current study to minimise the risk of Type I errors.

1.2.2. Challenges in Interpreting fMRI findings

The variant of fMRI used most commonly is blood oxygen-level-dependent (BOLD) imaging. This neuroimaging technique relies on the magnetic properties of haemoglobin to produce fMRI images. In brief, deoxygenated haemoglobin distorts its surrounding field, whereas oxygenated haemoglobin does not. Blood that contains a higher concentration of deoxygenated haemoglobin will produce a larger BOLD signal (Schleim & Roiser, 2009). The central tenet of this neuroimaging technique rests on the assumption that neuronal activity will result in increased oxygen consumption which is reflected in a larger BOLD signal (Heeger & Ress, 2002). Although studies have demonstrated that the BOLD signal correlates with synaptic activity (Logothetis et al., 2001), the BOLD signal is fundamentally an indirect measure of neuronal activity, through a cascade of physiological processes (Specht, 2020). These physiological processes, also known as vascular coupling, are subject to influence from a range of variables, over and above neuronal activation, such as blood pressure or blood oxygenation (Buxton, 2012; Buxton et al., 1998). Therefore, observed variation in a BOLD signal does not necessarily reflect the same degree of variation in neuronal activation (Specht, 2020). Furthermore, our understanding of the susceptibility of the BOLD signal to internal and external stimuli, and the relationship between the BOLD response and neuronal activation is currently limited (Curtis et al., 2016; Muller et al., 2012; Whitworth et al., 2005). Some studies have suggested that the BOLD signal is influenced by age or disease (D'Esposito et al., 2003), whereas others have suggested that stronger BOLD signals are actually associated with lower neural activation in some instances (Marcar et al., 2004). Others have argued that the BOLD signal likely varies within-individuals, and as such is not necessarily comparable between individuals (Specht, 2020). It is important to hold these issues in mind when evaluating findings in neuroimaging research. Further, it was important for me to keep this in mind when

writing up the results of my project. Although we examined BOLD responses in the ventral striatum during the anticipation of monetary gains in a reward-related paradigm and understood these to reflect neuronal activation underlying reward processing, there may be other factors influencing the variability of the BOLD signal. This may restrict the generalisability of our findings and may further preclude applying these findings on an individual level for diagnostic purposes.

1.2.3. Current Clinical Applications of fMRI

The translation of clinical neuroscience applies to two different outcomes. Firstly, a clinical concept may be translated into a quantifiable process using neuroimaging methods (Specht, 2020). For example, affective instability, that features prominently in bipolar spectrum disorder (BSD) may be investigated using fMRI to explore the neural mechanisms that may be underlying this phenomenon. In contrast, findings from neuroimaging may be translated into clinical practice. For example, the observation that people with BSD seem to display enhanced activation during processing of rewards (Nusslock & Alloy, 2017) may be used to inform clinical interventions where individuals are provided with psychoeducation materials and strategies to manage this theorised hypersensitivity tor rewards. Despite the intense interest and explosion of neuroimaging research over the past two decades, the translation of neuroimaging, and particularly, fMRI findings to clinical practice has been remarkably low (Schleim & Roiser, 2009).

Currently, the only routinely used clinical application of fMRI is presurgical mapping (Specht, 2020). This can be attributed to the challenges described above which further contribute to an absence of sufficient reliability in the measurement of individual activation strength (Holiga et al., 2018; Specht et al., 2003). In contrast, fMRI is frequently used to

explore differences in activation between groups of individuals such as those who present with the same psychiatric diagnosis (Fröhner et al., 2019). However, these investigations are further complicated by the heterogeneity of clinical populations. Psychopathology often occurs along a continuum where a diagnosis is given once an individual has crossed a threshold signifying a significant deviation from what is considered to be the norm (Stip & Letourneau, 2009). Studies of psychiatric populations are further complicated by variations in presentation relating to different subtypes subsumed under the same diagnosis, for example, bipolar type I, bipolar type II and cyclothymia. Moreover, the criteria used to diagnose disorders has undergone significant changes in the last two decades, and there may be further variation across different research groups and studies in the diagnostic criteria used to create psychiatric groups (Specht, 2020). Furthermore, fMRI currently has a limited capacity to discriminate individuals currently presenting with psychological distress or some form of psychopathology, from those without (Schleim & Roiser, 2009). In other words, although on average individuals with BSD may tend to report higher BOLD responses in the orbitofrontal cortex during anticipation of rewards (Nusslock & Alloy, 2017), this does not necessarily translate to the observation that every individual with BSD will show higher BOLD responses in the orbitofrontal cortex or that individuals with higher BOLD responses will have BSD.

Therefore, although fMRI studies examining differences in activation at the group level show a much higher reliability, a substantial amount of variation between different studies remains. Although MRI is used extensively in the field of neurology practice, it currently has limited applications in the field of clinical psychology and psychiatry (Specht, 2020). Thus, whilst the language used by many researchers in the field of clinical neuroscience denotes a relatively high degree of certainty, it is important to keep the above-mentioned challenges in mind. Findings linking neural activation and psychological processes have

already inspired practice applications such as lie detection and neurofeedback (Schleim & Roiser, 2009). However, it is imperative to reflect on the limitations of neuroimaging research to avoid harm due to misapplication or misunderstanding of findings (Schleim & Roiser, 2009). This is not just true of clinical neuroscience however and should be considered to be applicable to the field of psychological research in general.

1.3. The Value of Clinical Neuroimaging Research

Over the last decade, there has been a remarkable shift in the field of psychiatry and psychology, which has prompted many researchers and clinicians to propose a new framework for classifying psychiatric disorders (Nusslock & Alloy, 2017). This framework is based on core brain-behaviour dimensions. The Research Domain Criteria (RDoC; Insel et al., 2010) proposes that instead of beginning with a definition of a disorder that is grounded in clinical observations and then investigating the mechanisms underlying this disorder, we should begin with an understanding of brain-behaviour dimensions and subsequently tie these to specific symptoms (Krueger & DeYoung, 2016). One goal of the RDoC is to illuminate pathophysiological mechanisms that are transdiagnostic i.e., they are common to multiple forms of psychopathology (Insel et al., 2010; Krueger & DeYoung, 2016; Nusslock & Alloy, 2017). For example, although affective instability has traditionally been linked with borderline personality disorder, recent research has suggested that this phenomenon is a feature of many different forms of psychopathology. In support of this, the systematic review identified that affective instability is consistently reported across individuals with borderline personality disorder, BSD, and major depressive disorder. Thus, in this study, we adopted a transdiagnostic approach and examined processes that point to a particular deficit in the

Negative and Positive Valence Systems domains that appear to be common to all three forms of psychopathology.

The RDoC additionally aims to elucidate mechanisms that are distinct to specific forms of psychopathology and that reflect markers of differential vulnerability to these specific forms of psychopathology (Insel et al., 2010; Krueger & DeYoung, 2016). Importantly, this applies to specific symptoms and symptom profiles, in addition to forms of psychopathology (Krueger & DeYoung, 2016). For example, evidence suggests that certain mood disorders are typified by distinct and opposite profiles of rewarding processing (Nusslock & Alloy, 2017). BSD has typically been associated with hypersensitivity in reward systems, whereas in contrast, unipolar depression has been associated with hyposensitivity to rewards (Alloy et al., 2016). Thus, although dysregulated reward processing may be a feature that is common to both disorders, they are characterised by opposite profiles (Nusslock & Alloy, 2017). Clinical neuroscience offers the opportunity to explore whether these differences are borne out in the neural circuits that are typically involved in the processing of rewards, such as in the empirical study (Insel & Cuthbert, 2015). Where fMRI studies could further be of interest, is to examine neural mechanisms that are uniquely related to specific symptom constructs such as anhedonia or flight of ideas. In this way, one application of neuroimaging relates to the identification of biomarkers that confer differential vulnerability for specific forms of psychopathology or distinct psychopathological symptoms (Nusslock & Alloy, 2017).

Another interesting application of neuroimaging in the clinical domain, relates to discriminating individuals who will subsequently respond to treatment based on their BOLD responses. This can be applied to both the development of psychotropic medications and in the development of psychotherapeutic interventions. Whilst this represents an exciting avenue and some studies have reported promising findings (Fu et al., 2007; Seminowicz et al.,

2004), such studies are limited and have reported variable findings (Schleim & Roiser, 2009). Further, these studies have yet to be independently validated. As such, this application of neuroimaging to clinical practice is still in its infancy.

Whilst the above potential applications of clinical neuroimaging research are exciting avenues that prove to be very helpful in the future, throughout my involvement in this project, I have thought about how I can apply the outcome of my project to my clinical work with services users. Clinical neuroimaging enables us as clinicians to give more biologically grounded answers to questions of psychological functioning and distress, which can add information from a different perspective that can help to increase understanding (Gorgolewski & Poldrack, 2016). I have found that taking a biopsychosocial perspective, which views psychological functioning and distress as an interaction of biological, psychological, and social factors, has been helpful in working with clients. This was particularly the case during my placement at a gambling clinic where I included explanations of the reward system and the role of dopamine in addiction. Whilst this information did not resonate with all my clients, I do have memorable experiences of sessions in which this explanation created a light bulb moment that provided a deeper understanding of the mechanisms contributing to their difficulties, in addition to normalising and validating their experiences.

1.4. Concluding Reflections

Conducting this research project has been both a challenging and a rewarding experience. It has led me to reflect on a number of methodological and conceptual issues from the standpoint of a researcher and a clinician. It has further been a powerful experience to reflect on the challenges and limitations of neuroimaging and psychological research whilst actively engaged in my own research process. There is a potent pressure to produce novel

and exciting findings or as the saying goes “publish or perish” (Flournoy et al., 2020). This can contribute to the potential for ignoring, or being blind to limitations of the research process, and how these may be impacting your findings. In reflecting on the limitations of neuroimaging research, it can be easy to become pessimistic about the state of research in clinical neuroscience and psychological in general. It may also bring up questions about the value and translation of neuroimaging research in clinical practice. However, I would argue that clinical neuroscience has incredible potential in providing insights regarding the human brain and behaviour and translating these insights into clinical practice. Nevertheless, this requires acknowledgement of the issues and challenges within the field of neuroimaging, and further requires open and transparent research practices to facilitate critical examination and reproducibility.

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Appendices

Appendix A: Database Search Syntax

Search Terms	PsychInfo	Medline (OVID)	Web of Science
Short-term affect dynamics	Combined below sets of search terms (1-3) and Subject Headings (4 – 8) with OR 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 1 = (mood or mood adj3 instability or mood adj3 variability or mood adj3 reactivity or mood adj3 fluctuation* or mood adj3 inertia or mood adj3 autocorrelation or mood adj3 flexibility or mood adj3 lability or mood adj3 volatility or short-term mood dynamic* or short term mood dynamic*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 2 = (affect or affect* adj3 instability or affect* adj3 variability or affect* adj3 fluctuation* or affect* adj3 inertia or affect* adj3 autocorrelation or affect* adj3 flexibility or affect* adj3 lability or affect* adj3 volatility or affect* adj3 reactivity or short-term affect* dynamic* or short term affect* dynamic*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	Combined below sets of search terms (1-3) and Subject Headings (4 – 5) with OR 1 OR 2 OR 3 OR 4 OR 5 1 = (mood or mood instability or mood variability or mood reactivity or "fluctuations in mood" or mood inertia or mood autocorrelation or mood flexibility or mood lability or mood volatility or or short-term mood dynamic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 2 = (affect or affect* instability or affect* variability or affect* reactivity or "fluctuation* in affect* OR affect* inertia OR affect* autocorrelation OR affect* flexibility OR affect* lability OR affect* volatility OR variability in affect*" or short-term affect* dynamic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	Combined below sets of search terms with OR #1 OR #2 OR #3 #1 (((((((((ALL=(mood instability)) OR ALL=(mood variability)) OR ALL=(mood fluctuation*)) OR ALL=(mood inertia)) OR ALL=(mood autocorrelation)) OR ALL=(mood flexibility)) OR ALL=(mood lability)) OR ALL=(mood volatility)) OR ALL=(mood reactivity)) OR ALL=(short-term mood dynamic*) #2 (((((((((ALL=(affect* instability)) OR ALL=(affect* variability)) OR ALL=(affect* fluctuation*)) OR ALL=(affect* inertia)) OR ALL=(affect* autocorrelation)) OR ALL=(affect* flexibility)) OR ALL=(affect* lability)) OR ALL=(affect* volatility)) OR ALL=(affect* reactivity)) OR ALL=(short-term affect* dynamic*)

3 = (emotion or emotion* adj3 variability or emotion* adj3 instability or emotion* adj3 inertia or emotion* adj3 fluctuation* or emotion* adj3 autocorrelation or emotion* adj3 flexibility or emotion* adj3 lability or emotion* adj3 reactivity or emotion* adj3 volatility or or short-term emotion* dynamic* or short term emotion* dynamic*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] **Subject Headings** 4 = exp Emotional States/ 5 = exp emotions/ 6 = exp Emotional Instability/ 7 = emotional stability/ 8 = exp Emotional Responses/	3 = (emotion* or emotion* instability or emotion* variability or emotion* reactivity or "fluctuations in emotion*" or emotion* inertia or emotion* autocorrelation or emotion* flexibility or emotion* lability or emotion* volatility or or short-term emotion* dynamic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] **Subject Headings** 4 = exp Affect/ 5 = exp Emotions/	#3 (((((((((ALL=(emotion* instability)) OR ALL=(emotion* variability)) OR ALL=(emotion* fluctuation*)) OR ALL=(emotion* inertia)) OR ALL=(emotion* autocorrelation)) OR ALL=(emotion* flexibility)) OR ALL=(emotion* lability)) OR ALL=(emotion* volatility)) OR ALL =(emotion* reactivity)) OR ALL=(short-term emotion* dynamic*)

1.	**Ecological momentary assessment**	Combined below sets of search terms (1-9) and Subject Headings (10) with OR 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 1 = ecological momentary assessment.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 2 = experience sampling.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 3 = time series analysis.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 4 = ("event-contingent " or "event contingent ").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 5 = EMA.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 6 = ESM.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 7 = Daily measure* AND affect* AND (instability OR variability)	Combined below sets of search terms (1-9) and Subject Headings (10) with OR 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 1 = ecological momentary assessment.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 2 = experience sampling.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 3 = time series.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 4 = ("event-contingent sampling" or "event contingent sampling").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 5 = EMA.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 6 = ESM.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 7 = Daily measure* AND affect* AND (instability OR variability)	**#4 ((((((ALL = (ecological momentary assessment)) OR ALL = (EMA)) OR ALL = (experience sampling)) OR ALL = (ESM)) OR ALL = (time series)) OR ALL = (event contingent))**

8 = Daily mood rating* AND (variability OR instability)	8 = Daily mood rating* AND (variability OR instability)
9 = Visual analogue scale AND mood AND (variability OR instability)	9 = Visual analogue scale AND mood AND (variability OR instability)
Subject Headings	**Subject Headings**
10 = exp Ecological Momentary Assessment/	10 = exp Ecological Momentary Assessment/

2.	**Mood disorders**	Combined below sets of search terms (1-12) and Subject Headings (13 – 22) with OR 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 1 = bipolar disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 2 = depressi* disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 3 = mania.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 4 = depressi*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 5 = major depressi* disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 6 = manic.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 7 = hypomania.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	Combined below sets of search terms (1-12) and Subject Headings (13 – 19) with OR 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 1 = bipolar disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 2 = depressi* disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 3 = mania.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 4 = depressi*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 5 = major depressi* disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 6 = manic.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 7 = hypomania.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	**#5 ((((((((((ALL=(bipolar disorder*)) OR ALL=(depression)) OR ALL=(major depressi* disorder*)) OR ALL=(borderline personality disorder*)) OR ALL=(hypomania)) OR ALL=(hypomanic)) OR ALL=(mania)) OR ALL=(manic)) OR ALL=(depressi* disorder*)) OR ALL=(depressive)) OR ALL=(emotionally unstable personality disorder*)) OR ALL=(mood disorder*)) OR ALL=(affect* disorder*)**

8 = hypomanic.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

9 = borderline personality disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

10 = emotionally unstable personality disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

11 = mood disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

12 = affect* disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

Subject Headings

13 = exp Bipolar Disorder/
14 = exp Bipolar I Disorder
15 = exp Bipolar II Disorder
16 = exp Major Depression/
17 = exp Mania/
18 = exp Hypomania/
19 = exp Affective Disorders/
20 = exp Borderline Personality Disorder/
21 = exp “Depression (emotion)”/
22 = exp Borderline states/

8 = hypomanic.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

9 = borderline personality disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

10 = emotionally unstable personality disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

11 = mood disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

12 = affect* disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]

Subject Headings

13 = exp Bipolar Disorder/
14 = exp Depressive Disorder, Major/
15 = exp Depressive Disorder/
16 = exp Mania/
17 = exp Mood Disorders/
18 = exp Depression/
19 = exp Borderline Personality Disorder/

3.	**Combination**	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8) AND (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10) AND (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22)	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8) AND (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10) AND (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19)	(**#1 OR #2 OR #3) AND (#4) AND (#5)**

Appendix B: Details of Additional Findings in Systematic Review

Study	Primary clinical group	Comparison group	Measure of Affect Dynamics	Other Measures Included in Analyses	Additional Findings
1. Bomyea et al. (2021)	BSD (*n* = 46)	HC (*n* = 20)	Instability: MSSD	Depressive and manic symptoms; Performance on range of cognitive tests	In comparison to HC, BSD group showed worse cognitive performance on lab tests. BSD group showed worse cognitive performance on mobile tests relative to HC. BSD group reported lower levels of energy and greater levels of sadness in comparison to HC. In BSD group, mobile ratings of mania and sadness earlier in the day were associated with worse processing speed and increased working memory performance respectively, on next mobile cognitive test. Greater stress was associated with better working memory, and higher levels of happiness were associated with better processing speed within the same mobile test.
2. Bowen et al. (2017)	Depression (*n* = 74)	HC (*n* = 59)	Instability: MSSD	Mean levels of negative and positive affect.	Depressed group experienced more severe low moods and less severe high moods. Mean low mood and mean high mood were significantly associated in the depressed group indicating that this group experienced negative affect concurrently with positive affect.
3. Cowdry et al. (1991)	UD (*n* = 10)	BPD (*n* = 16) PMS (*n* = 15) HC (*n* = 24)	Variability: Within-person SD, day-to-day Within-day Inertia: autocorrelation	Temporal trends in affect dynamics.	PMS group reported mean affect ratings that were comparable to the HC, however, they reported greater variability in affect. Morning-to-morning affect variability in PMS group was higher than HC but random variability ratio was lowest, and this group reported significantly higher autocorrelation in comparison to other groups; each morning affect rating was more closely associated with previous day's rating in PMS group in comparison to other groups.

4. Crowe et al. (2019)	UD (*n* = 31)	HC (*n* = 33)	Variability: Within-person SD Instability: MSSD	Self-esteem, suicidality, tiredness	UD group exhibited increased variability and instability in self-esteem and passive suicidality and decreased variability in tiredness in comparison to HC. Instability of self-esteem could not be accounted for by mean symptom levels. Instability in suicidality was associated with mean symptom levels; as severity of suicidality increased, so did instability. Diurnal time-trends were observed in positive affect, tiredness, suicidality and self-esteem.
6. Ebner-Priemer et al. (2007)	BPD (*n* = 50)	HC (*n* = 50)	Instability: MSSD	Distress	BPD group exhibited heightened affect instability for both valence and distress dimensions in comparison to HC group. Heightened affect instability was characterised by sudden large decreases in positive mood states. Nearly half of these decreases were so large they resulted in a negatively valenced state.
7. Gershon et al. (2012)	BSD-I (*n* = 32)	HC (*n* = 36)	MSSD Instability:	Sleep	Longer sleep onset latency was more strongly coupled with higher negative affect in BSD group in comparison to HC. Longer wakefulness after sleep onset and lower sleep efficiency were more strongly coupled with higher negative affect in BSD group in comparison to HC. No significant differences were observed between groups in degree of coupling between any measures of sleep and positive affect.
8. Golier et al. (2001)	PTSD (*n* = 15)	UD (*n* = 17) HC (*n* = 17)	Variability: Within-person SD	PTSD psychopathology	UD and PTSD groups reported comparable levels of depression. PTSD group exhibited increased affective variability in comparison to UD group. No significant differences were observed for affective variability between PTSD and HC group. PTSD group reported higher levels of anxiety in comparison to UD group but there were no group differences in variability of anxiety.

9. Hall et al. (1991)	Depressive disorder (*n* = 9)	HC (*n* = 9)	Variability: Within-person SD	Temporal trends in affective variability	Both groups' moods varied in an ultradian and circadian cycles, however, the depressed group reported ultradian rhythms of greater amplitude. There were no significant differences in cycle period between the groups, thus, differences in ultradian cycle amplitude, not period, accounts for increased variability of affect in depressed group.
10. Heininga et al. (2019)	UD (*n* = 47)	HC (*n* = 44)	Variability: Within-person variance Instability: RMSSD Inertia: autocorrelation	Affective reactivity to rewards; affect dynamics and anhedonia	Anhedonia was associated with low levels of positive affect but not altered positive affect dynamics. UD group did not report differences in frequency of rewards in daily life. UD group did not report statistical differences in positive affect reactivity and recovery.
11. Houben et al. (2016)	BPD (*n* = 34)	HC (*n* = 28)	Variability: Within-person SD Instability: MSSD	Emotional switching	BPD group was not characterised by higher propensity to switch emotions in comparison to HC group but did exhibit larger emotional changes from one time point to the next if they switched between states of opposite valence. BPD group tended to make large emotional changes in concordance with switches between states of opposite emotional valence.
12. Köhling et al. (2016)	UD and BPD (*n* = 20)	UD (*n* = 21)	Instability: SSD	Occurrence of positive and negative events and affective reactivity to these events	BPD with comorbid depression reported decreased perceived affective reactivity to events in comparison to BPD group. No significant differences in associations between events and affect were observed between groups apart from the event of being along, which was significantly associated with lower mood in BPD with comorbid depression group.

13. Lamers et al. (2018)	BSD-I (*n* = 33)	BSD-II (*n* = 37) UD (*n* = 116) Anxiety disorder (*n* = 36) HC (*n* = 65)	Variability: within-person SD Instability: MSSD Inertia: Autocorrelation	Occurrence of positive and negative events.	BSD-I group reported greater decreases in sad and anxious mood after positive events in comparison to HC. UD group reported greater decreases in anxious mood following positive events in comparison to HC. BSD-II, UD and anxious groups reported greater increases in anxious mood following negative events. No differences were reported in sad mood. Increased affect variability and instability was associated with decreased psychological wellbeing. Greater instability of affect was associated with comorbid anxiety disorders.
14. Li et al. (2019)	BSD (*n* = 10)	HC (*n* = 10)	Variability: Within-person SD	Energy, speed of thought, impulsivity, social stress.	The BSD group reported significantly elevated variability within energy, speed of thought, impulsivity, pain and perception of skill of tasks. Increased BSD symptoms in the evening were associated with reduced sleep time that night. Pain, social stress, perception of skill, effort and task-preference were associated with worsening of BSD symptoms.
15. Lovejoy and Steuerwald (1995)	Cyclothymia (*n* = 12)	Intermittent depression (*n* = 16) HC (*n* = 19)	Variability: Within-person SD	Trait level of positive and negative affect.	Depressed group reported significantly lower levels of trait positive affect in comparison to HC group. Bipolar group reported significantly higher levels of trait of positive affect in comparison to HC group.
16. McGowan et al. (2021)	BSD (*n* = 38)	BPD (*n* = 25) HC (*n* = 43)	Instability: RMSSD	Blood pressure, depressive symptoms, manic symptoms.	BSD group had significantly wider resting pulse pressure in comparison to BPD and HC groups. No group differences were observed for measures of heart rate, systolic BP, diastolic BP or mean arterial blood pressure. Measures of blood pressure and affective instability were inversely related. Higher resting heart rate was associated with increased instability for negative affect.

17. Mneimne et al. (2018)	BPD (*n* = 38)	BSD (*n* = 14) UD (*n* = 15) HC (*n* = 62)	Instability: MSSD Inertia: modelled as extent to which an emotion at any given time maintained at next report	Affective reactivity to interpersonal challenges.	BPD group exhibited heightened levels of reactivity in the domains of guilt, shame and excitement in response to interpersonal challenges including rejection, betrayal, abandonment, offense, disappointment, and self-image challenge. Heightened levels of reactivity in irritability and happiness were observed across all clinical groups.
18. Moukhtarian et al. (2021)	BPD (*n* = 19)	ADHD (*n* = 28) ADHD and BPD (*n* = 22) HC (*n* = 29)	Instability: SSD	Occurrence of negative events.	Comorbid BPD and ADHD group exhibited significantly higher instability of negative affect and reported less positive and more negative intensity of affect in comparison to HC. ADHD group reported increased intensity of specific negative affect items e.g., irritability and exhibited increased instability of negative affect in comparison to HC group. No differences were observed in intensity of positive affect between ADHD and HC. No differences were observed in instability of positive affect between ADHD and HC. Depressive and anxious symptoms were strongly associated with intensity and instability of affect in both BPD and ADHD groups.
19. Napolitano et al. (2021)	BPD (*n* = 56)	Community controls (*n* = 60)	Instability: SSD	Personality traits, impulsivity, interpersonal disagreements, close social contact.	BPD group reported higher levels of disagreements, increased neuroticism, and lower agreeableness, conscientiousness, and extraversion. Extraversion and neuroticism predicted increases in instability of negative affect whereas openness predicted decreases in instability of negative affect.
20. Ortiz et al. (2015)	BSD (*n* = 30)	HC (*n* = 30)	Variability: Entropy calculations	Relationships between anxiety, sleep and mood	Higher anxiety levels were significantly correlated with lower mood across both groups and no statistical differences were found between groups. HC. Increased sleep time was associated with higher mood in HC, whereas the opposite was true in BSD group.

21. Peeters et al. (2006)	UD (*n* = 47)	HC (*n* = 39)	Variability: Within-person SD	Diurnal variation in affect dynamics	UD group exhibited increasing levels of positive affect during the day with the peak in positive affect occurring later in the day. UD group exhibited a more pronounced diurnal rhythm in negative affect that decreased over the course of the day and was more variable from moment-to-moment in comparison to HC.
22. Pincus et al. (2008)	PMDD (*n* = 15)	Recurrent depressive disorder (*n* = 9) HC (*n* = 8)	Variability: Within-person SD Day-to-day variance Within-day variance Diurnal variation	PMDD psychopathology	HC group could be differentiated from PMDD group on the basis of variability, irregularity, and spikiness of affect. PMDD group could be differentiated from RBD group on these measures. PMDD group exhibited the most variability of affect and HC group exhibited the least. Significant differences were further observed in irregularity and spikiness; in both cases, PMDD reported the smallest values.
23. Russell et al. (2007)	BPD (*n* = 30)	HC (*n* = 44)	Variability: Flux (within-person SD)	Interpersonal behaviour	BPD group reported increased levels of negatively valenced affect. BPD group was less dominant, more submissive, more quarrelsome, and more extreme in overall levels of behaviour in comparison to HC. BPD group reported more variability in dominant, quarrelsome, and agreeable behaviours, and showed a higher degree of behavioural spin in comparison to HC.
24. Santangelo et al. (2020)	BPD (*n* = 60)	Remitted BPD (*n* = 35) HC (*n* = 60)	Instability: SSD, PAC, APPC	Self-esteem	BPD group reported higher levels of self-esteem instability in comparison to HC group. Self-esteem instability and affect instability were highly correlated in both groups but affect instability was not solely explained by self-esteem instability. Both self-esteem instability and affect instability were related to level of general psychopathology in BPD group.

25. Santangelo et al. (2018)	BPD (*n* = 130)	HC (*n* = 130)	Instability: SSD	Age	Lower affective instability was associated with greater age among BPD participants. Instability of valence and tense arousal were observed to significantly decrease across the age span in BPD but not HC groups. Controlling for comorbidity and severity of BPD symptoms did not change the findings.
26. Santangelo et al. (2017)	BPD (*n* = 60)	HC (*n* = 60)	Instability: SSD, PAC, APPC	Self-esteem	BPD group reported elevated levels of instability of self-esteem. Self-esteem instability and affective instability were highly correlated in BPD group. Both types of instability were associated with general levels of psychopathology. Neither self-esteem nor affective instability could fully explain one another nor psychopathology completely, suggesting that they represent unique facets of BPD.
27. (Santangelo et al., 2014)	BPD (*n* = 43)	PTSD (*n* = 28) Bulimia nervosa (*n* = 20) HC (*n* = 28)	Instability: MSSD, PAC	PTSD and BN psychopathology	No significant differences were observed in affect instability across the clinical groups. Controlling for mean levels of valence and distress did not change the findings.
Scheiderer et al. (2016)	BPD (*n* = 78) (33 also met criteria for PTSD)	UD/Dysthymia (*n* = 50)	Instability: MSSD, detrended MSSD	Impact of PTSD comorbidity on affective instability	BPD individuals with comorbid PTSD reported the highest affect instability across all subgroups. This group reported greater instability for fear and sadness in comparison to BPD individuals without comorbid PTSD. UD/DYS individuals with comorbid PTSD reported lower levels of instability for fear and sadness in comparison to individuals with no comorbid PTSD. PTSD comorbidity was not associated with altered affect instability of negative affect, hostility or positive affect in either BPD or UD/DYS groups.

30. Servaas et al. (2017)	UD (*n* = 62)	HC (*n* = 41)	Instability: MAASD	Positive and negative cognition, resting-state fMRI	UD group had fewer connections between default mode subnetwork and other subnetworks. UD individuals who showed more instability in feeling down exhibited fewer connections between the salience/reward subnetwork and other subnetworks, whereas those who exhibited more instability in feeling irritated displayed higher local efficiency coefficients in the frontoparietal subnetwork neural network.
31. Snir et al. (2017)	Avoidant personality disorder (*n* = 43)	BPD (*n* = 57) HC (*n* = 53)	Instability: MSSD, PAC	APD psychopathology	APD group exhibited higher levels of affect instability in comparison to HC group but significantly less affect instability in comparison to BPD group. 82.5% of individuals in BPD group were above the threshold for the borderline affective instability criterion, in comparison to 9.3% of individuals in the APD group.
33. Stein (1995)	BPD (*n* = 15)	Anorexia nervosa (*n* = 4) HC (*n* = 10)	Variability: Within-person SD	AN psychopathology	AN group reported significantly higher levels of unpleasant and unpleasant activated affect states and greater variability in unpleasant affect in comparison to both BPD and HC groups. AN group further reported lower levels of pleasant and activated pleasant affects and decreased variability in unactivated pleasant affect states in comparison to HC group. No differences were observed in persistence of unpleasant affect states over time between BPD and HC or AN. AN exhibited significantly more persistence of unactivated unpleasant affect in comparison to HC.
34. Stein (1996)	BPD (*n* = 15)	Anorexia nervosa (*n* = 4) HC (*n* = 10)	Variability: Within-person SD	Unity of self-concept	Unity of self-concept was a significant predictor of instability of negative affect. Participants with a highly unified or interdependent collection of self-defining attributes experienced significantly higher levels of variability of negative affect.

35. Thompson et al. (2012)	UD (*n* = 53)	HC (*n* = 53)	Variability: Within-person SD Instability: MSSD Inertia: autocorrelation	Occurrence of and intensity of significant events	UD group reported greater levels of reactivity of negative affect to positive events but comparable levels of reactivity to negative events to HC. Average levels of negative affect, frequency or intensity of events could account for group differences in instability of negative affect. No significant differences were observed in levels of reactivity to positive and negative events in comparison to HC.

Note.

ADHD: attention deficit hyperactivity disorder; ASPD: antisocial personality disorder; BSD: bipolar spectrum disorder; BSD-I: bipolar disorder type I; BSD-II: bipolar disorder type II; BPD: borderline personality disorder; GAD: generalized anxiety disorder; HC: healthy controls; UD: unipolar depression; PMDD: premenstrual dysphoric disorder; PMS: premenstrual syndrome; PTSD: post-traumatic stress disorder

AAC: adjusted acute change; APPC: aggregated point-by-point change; ASSD: squared successive difference; MAASD: mean-adjusted absolute successive difference; MSSD: mean squared successive difference; PAC: probability of acute change; RMSSD: root mean squared successive difference; SD: standard deviation; SSD: squared successive difference

Appendix C: Further Details of Quality Control Procedures Employed in Studies in Systematic Review

Study	Recruitment method	Did study control for backfilling (if paper and pen modality used)	EMA/ESM compliance rate reported	Retention rate reported	Missing data reported	Reported on how missing data was dealt with	Controlled for mean level of affect
1. Bomyea et al. (2021)	Community	N/A	Yes	No	No	No	Not reported
2. Bowen et al. (2017)	Outpatient clinical setting	Not reported	No	No	No	No	Not reported
3. Cowdry et al. (1991)	Participating in other studies at National Institute of Mental Health	Not reported	No	No	No	No	Not reported
4. Crowe et al. (2019)	Inpatient and outpatient clinical setting, and community	Matching self-reported time of completion of survey with pre-programmed time of each signal.	Yes	Yes	Yes	No	Yes
5. Ebner-Priemer et al. (2015)	Outpatient and inpatient settings, and national register	N/A	No	Yes	No	No	Not reported
6. Ebner-Priemer et al. (2007)	Not reported for clinical group	N/A	Yes	No	Yes	No	Not reported
7. Gershon et al. (2012)	Community	Participants required to call in after completion of report	No	No	No	No	Not reported

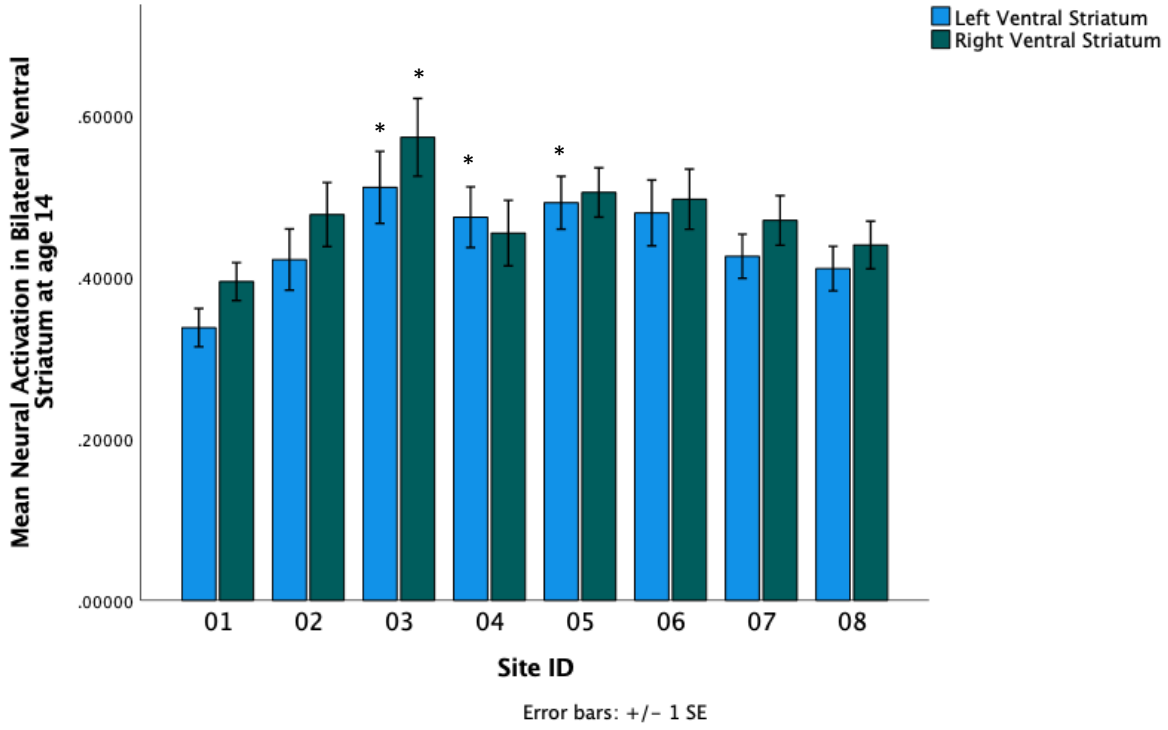
8. Golier et al. (2001)	Outpatient setting	Administered by researchers	No	No	No	No	Not reported
9. Hall et al. (1991)	Inpatient setting	Administered by researchers	Yes	Yes	Yes	No	Not reported
10. Heininga et al. (2019)	Inpatient setting and community	N/A	Yes	Yes	No	No	Not reported
11.Houben et al. (2016)	Inpatient setting and community	N/A	Yes	Yes	Yes	No	Not reported
12. Köhling et al. (2016)	Inpatient and outpatient setting	N/A	Yes	Yes	Yes	No	Not reported
13. Lamers et al. (2018)	Community and other sources to enrich sample for mood disorders	N/A	Yes	No	Yes	No	Not reported
14. Li et al. (2019)	Not reported	N/A	No	No	No	No	Not reported
15. Lovejoy and Steuerwald (1995)	Undergraduates	Not reported	Yes	No	Yes	No	No
16. McGowan et al. (2021)	Community, outpatient services, study registration lists	N/A	No	Yes	No	Yes	Not reported

17. Mneimne et al. (2018)	Community and outpatient clinics	N/A	Yes	No	No	No	Not reported
18. Moukhtarian et al. (2021)	Outpatient clinics and community	N/A	Yes	Yes	No	No	Not reported
19. Napolitano et al. (2021)	Outpatient clinics and community	N/A	Yes	No	No	No	Not reported
20. Ortiz et al. (2015)	Outpatient setting	Not reported	Yes	Yes	Yes	Yes	Not reported
21. Peeters et al. (2006)	Outpatient clinical setting	Not reported	Yes	Yes	Yes	No	Not reported
22. Pincus et al. (2008)	Community	Not reported	No	No	No	No	Not reported
23. Russell et al. (2007)	Outpatient clinical and community	Forms returned the following day	Yes	No	No	No	Yes
24. Santangelo et al. (2014)	Outpatient and inpatient clinical settings	N/A	Yes	No	Yes	No	Yes
25. Santangelo et al. (2020)	Clinic and random selection from national register	N/A	Yes	No	Yes	No	Not reported
26. Santangelo et al. (2018)	Outpatient setting and national register	N/A	Yes	No	Yes	No	Not reported
27. Santangelo et al. (2017)	Inpatient setting and national register	N/A	Yes	No	Yes	No	Yes

28. Scheiderer et al. (2016)	Outpatient clinics	N/A	Yes	No	Yes	No	Not reported
29. Scott et al. (2020)	Community-based; stratified, random household sampling	N/A	Yes	No	No	Yes	Not reported
30. Servaas et al. (2017)	Previous studies, outpatient settings, community	N/A	Yes	Yes	Yes	No	Not reported
31. Snir et al. (2017)	Community	N/A	Yes	Yes	No	No	Not reported
32. Sperry et al. (2020)	University setting	N/A	No	Yes	No	Yes	Not reported
33. Stein (1995)	Inpatient psychiatric units	Collecting completed diaries every 3 days	Yes	Yes	No	No	Not reported
34. Stein (1996)	Inpatient psychiatric units	Collecting completed diaries every 3 days	Yes	Yes	Yes	No	Not reported
35. Thompson et al. (2012)	Community	N/A	Yes	Yes	Yes	Yes	Yes
36. Trull et al. (2008)	Outpatient setting	N/A	Yes	Yes	Yes	No	Not reported
37. Tsanas et al. (2016)	Not reported	N/A	Yes	Yes	No	Yes	Not reported
38. van de Leemput et al. (2014)	Population-based sample	Not reported	No	No	No	No	Not reported

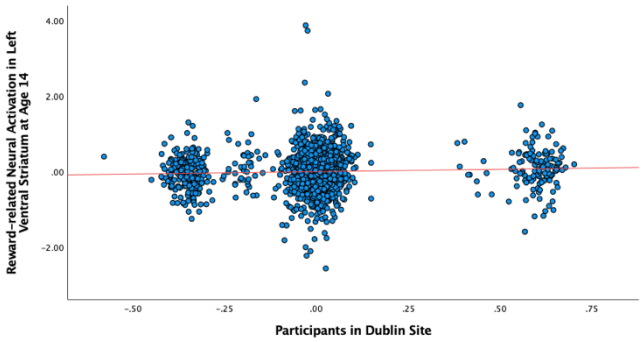
Appendix D: Associations Between Demographic and Clinical Variables and Neural Activation in Bilateral Ventral Striatum at age 14

Figure 1.
Bar Chart of Mean Reward-related Neural Activation in Bilateral Ventral Striatum age 14 and site ID

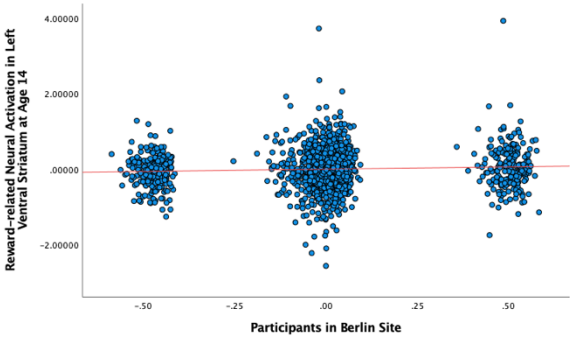


Dublin site was significantly associated with higher reward-related activation in bilateral VS at age 14; Left VS: β = .066, *p* = .031; Right VS: β = .085, *p* = .006
Berlin site was significantly associated with higher reward-related activation in bilateral VS at age 14; Left VS: β = .079, *p* = .015
Hamburg site was significantly associated with higher reward-related activation in bilateral VS at age 14; Left VS: β = .068, *p* = .036
Note. ID_01: London; ID_02: Nottingham; ID_03: Dublin; ID_04: Berlin; ID_05: Hamburg: ID_06: Mannheim; ID_07: Paris
Error bars represent ± 1 standard error

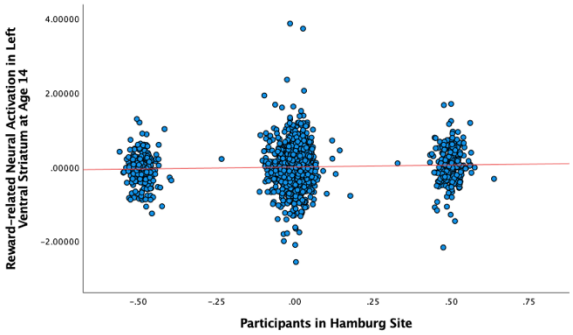
Figure 2.
Partial Regression Plots of Mean Reward-related Neural Activation in Bilateral Ventral Striatum age 14 and site ID



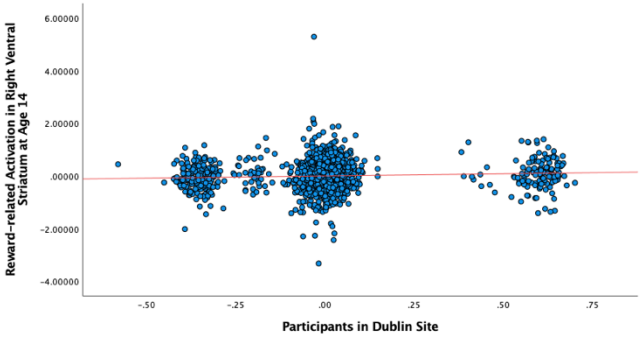
2a Participants in Dublin site had higher activations in left VS at age 14.
β = .066, *p* = .031



2b Participants in Berlin site had higher activations in left VS at age 14.
β = .079, *p* = .015



2c Participants in Hamburg site had higher activations in left VS at age 14.
β = .068, *p* = .036



2d Participants in Dublin site had higher activations in left VS at age 14.
β = .085, *p* = .006

Appendix E: Results of Cross-Sectional Analyses Excluding Participants Currently Taking Psychotropic Medication

Table 1.
Results of Hierarchical Regression Analyses for the Activations of the Bilateral Ventral Striatum and the Depression Symptom Score, (Hypo)manic Symptom Score and Depression (Hypo)manic Symptom Interaction at Age 14 Excluding Participants Currently Taking Psychotropic Medication (*n* = 1614)

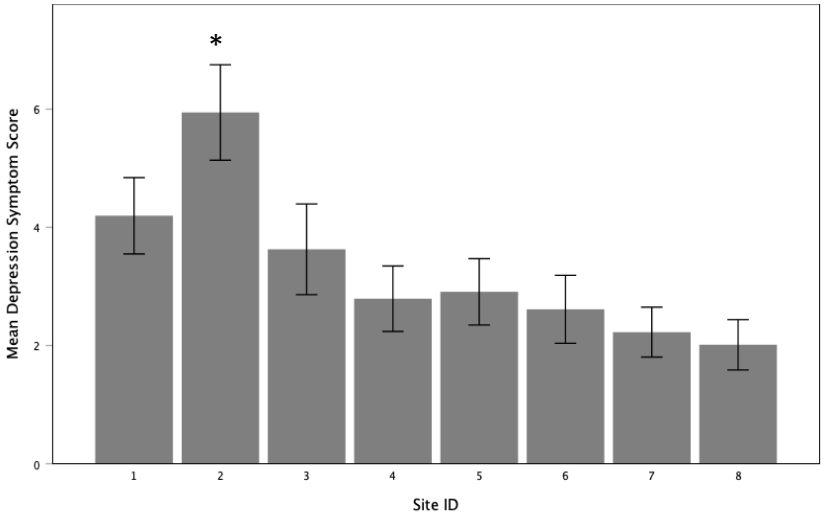
	DV Reward-related activation (Left VS)			DV Reward-related activation (Right VS)		
	β	*t*	*p*	β	*t*	*p*
Step 1: Mood Symptoms						
Depression	-.044	-1.037	.300	-.014	-.343	.731
(Hypo)manic	-.025	-.833	.405	-.002	-.057	.954
Interaction	.013	.271	.786	-.021	-.434	.665
	R^2 = .002, $F_{3, 1610}$ = 1.147 p = .329			R^2 = .001, $F_{3, 1610}$ = .626, p = .598		
Step 2: Demographics						
Depression	-.033	-.773	.440	-.011	-.261	.794
(Hypo)manic	-.030	-.992	.321	-.003	-.082	.935
Interaction	.014	.291	.771	-.021	-.439	.661
Age	-.018	-.735	.462	-.005	-.204	.839
SES	.024	.943	.346	.002	.081	.936
Gender	.004	.167	.867	-.007	-.295	.768
ID_01	-.034	-1.029	.304	-.013	-.409	.683
ID_02	.013	.372	.710	.042	1.254	.210
ID_03	.060	1.974	**.049***	.079	2.627	**.009****
ID_04	.071	2.181	**.029***	.042	1.275	.203
ID_05	.062	1.908	**.**057	.051	1.550	.121
ID_06	.056	1.741	.082	.044	1.355	.176
ID_07	.016	.472	.637	.042	1.259	.208
	R^2 = .014, $F_{10, 1600}$ = 1.927 p = **.038***			R^2 = .009, $F_{10, 1600}$ = 1.204, p = .284		
Step 3: Non-Clinical Factors						
Depression	-.032	-.766	.444	-.012	-.273	.785
(Hypo)manic	-.031	-1.011	.312	-.005	-.148	.882
Interaction	.014	.284	.776	-.020	-.422	.673
Age	-.020	-.784	.433	-.008	-.329	.742
SES	.022	.826	.409	.000	-.008	.994
Gender	.005	.207	.836	-.007	-.274	.784
ID_01	-.029	-.896	.370	-.011	-.339	.735
ID_02	.017	.508	.611	.044	1.296	.195

ID_03	.066	2.144	**.032***	.084	2.713	**.007****
ID_04	.074	2.270	**.023***	.044	1.329	.184
ID_05	.065	1.978	**.048***	.053	1.607	.108
ID_06	.059	1.817	.069	.045	1.380	.168
ID_07	.020	.602	.547	.045	1.361	.174
Pubertal Status	.013	.511	.610	.028	1.105	.269
Intelligence Estimate	.025	.970	.332	.012	.460	.645
	R^2 = .015, $F_{2, 1598}$ = .587 p = .556			R^2 = .0.009, $F_{2, 1598}$ = .702, p = .496		
Step 4: Clinical Factors						
Depression	-.032	-.751	.453	-.013	-.297	.766
(Hypo)manic	-.031	-.999	.318	-.005	-.178	.859
Interaction	.015	.313	.754	-.021	-.442	.658
Age	-.018	-.719	.472	-.009	-.339	.735
SES	.020	.771	.441	-.001	-.042	.967
Gender	.008	.313	.755	-.006	-.252	.801
ID_01	-.029	-.872	.383	-.011	-.342	.732
ID_02	.017	.482	.630	.043	1.255	.210
ID_03	.065	2.104	**.036***	.086	2.749	**.006****
ID_04	.076	2.320	**.020***	.044	1.329	.184
ID_05	.065	1.996	**.046***	.053	1.610	.108
ID_06	.057	1.770	.077	.044	1.357	.175
ID_07	.025	.760	.447	.046	1.380	.168
Pubertal Status	.016	.633	.527	.025	.993	.321
Intelligence Estimate	.018	.706	.480	.012	.446	.656
Monthly Alcohol Use	.018	.677	.498	.029	1.080	.280
Daily Cigarette Use	-.024	-.881	.379	-.008	-.275	.784
Lifetime Drug Use	-.050	-1.786	.074	-.008	-.279	.780
Novelty-Seeking	.017	.664	.507	.000	-.015	.988
	R^2 = .019, $F_{4, 1594}$ = 1.550 p = .185			R^2 = 0.01, $F_{4, 1594}$ = .317, p = 0.867		

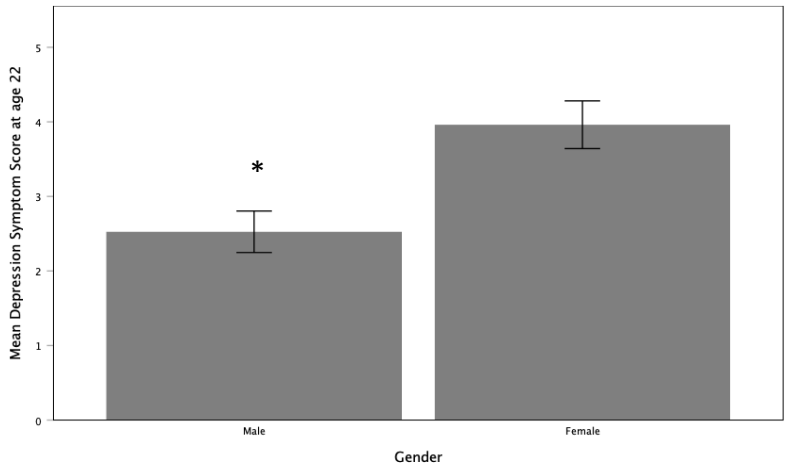
Note. All reported β estimates are standardized regression coefficients. n = 1614
New variables added in each step of model building are bolding to aid the reader.
ID_01: London; ID_02: Nottingham; ID_03: Dublin; ID_04: Berlin; ID_05: Hamburg: ID_06: Mannheim; ID_07: Paris
The VS activation was from the contrast of large-win vs. no-win.
VS, ventral striatum
*p < .05
**p < .01
Significant findings are bolded to aid the reader.

Appendix F: Association Between Demographic and Clinical Variables and Mood Symptom Score at Follow-up

Figure 3.
Bar Charts of Depression Symptom Score at age 22 and Demographic Variables

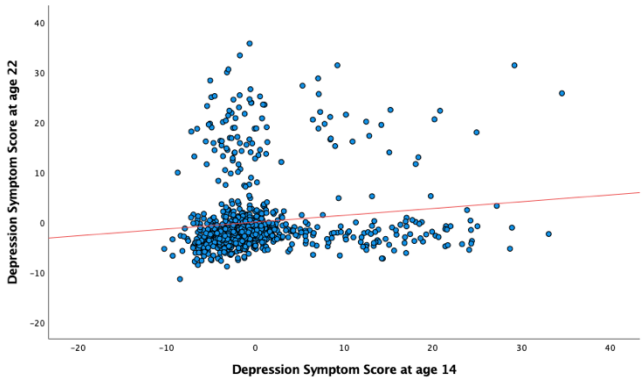


3a. Bar Chart of Mean Depression Symptom Score and Site ID
Nottingham site was significantly associated with higher depression symptom scores
$\beta = .169$, $p < .001$
Note. ID_01: London; ID_02: Nottingham; ID_03: Dublin; ID_04: Berlin; ID_05: Hamburg: ID_06: Mannheim; ID_07: Paris
Error bars represent ± 1 standard error

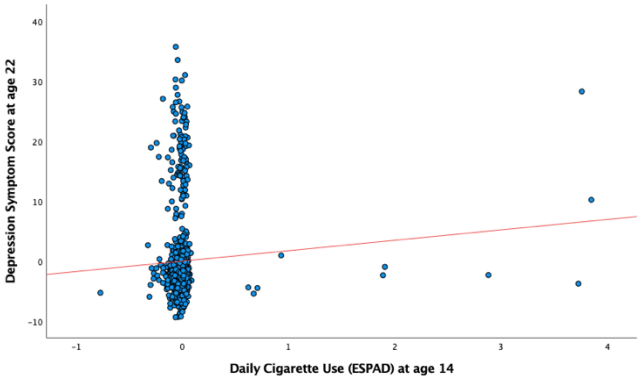


3b. Bar Chart of Mean Depression Symptom Score and Gender
Male participants reported significantly lower levels of depressive symptoms.
$\beta = -.097$, $p = .002$
Note.
Error bars represent ± 1 standard error

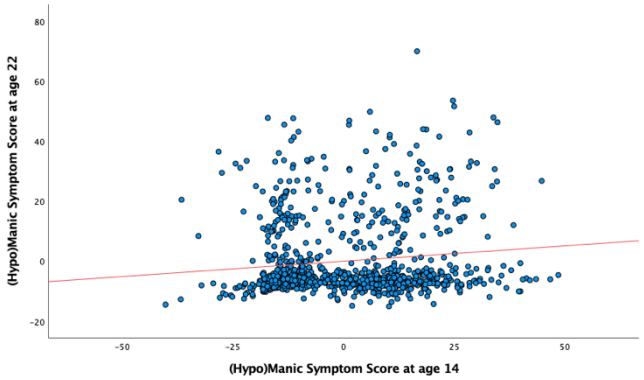
Figure 4.
Partial Regression Plots of Mood Symptom Score at age 22 and Clinical Variables at age 14



2a Partial Regression Plot of Depression Score at 22 and Depression Score at 14
Higher levels of depressive symptoms at age 14 were significantly associated with higher levels of depressive symptoms at age 22
$\beta = .128$, $p < .001$



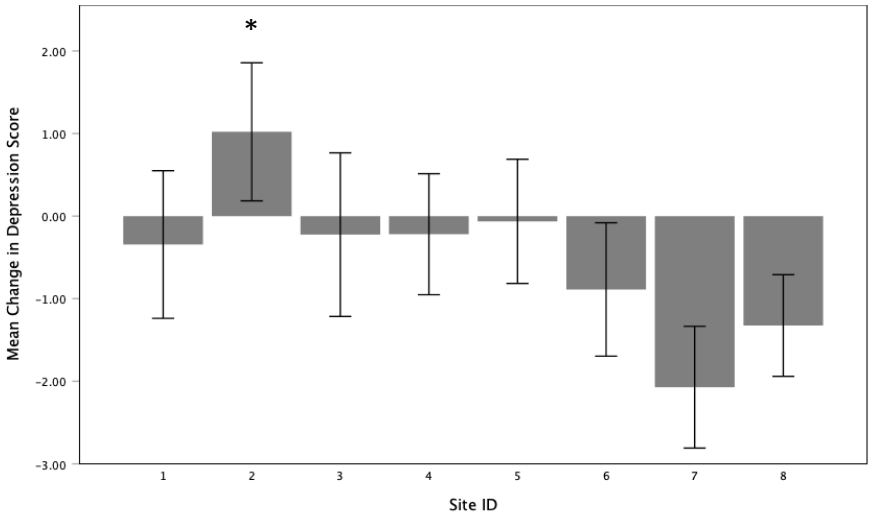
2b Partial Regression Plot of Depression Score at 22 and Daily Cigarette Use at 14
Smoking more cigarettes per day at age 14 was significantly associated with higher levels of depressive symptoms at age 22
$\beta = .064$, $p = .046$



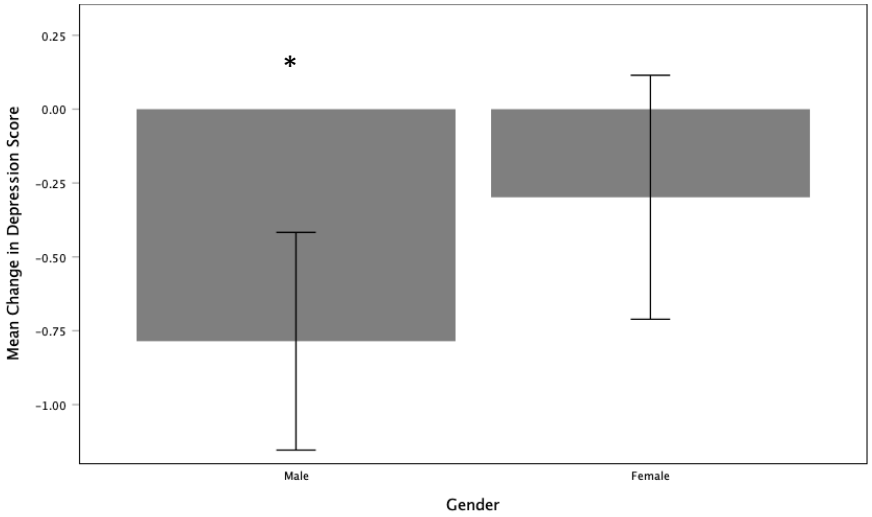
2c Partial Regression Plot of (Hypo)Manic Score at 22 and (Hypo)Manic Score at 14
Higher levels of (hypo)manic symptoms at age 14 were significantly associated with higher levels of (hypo)manic symptoms at age 22
$\beta = .126$, $p < .001$

Appendix G: Association Between Demographic and Clinical Variables and Change in Mood Symptom Score from Baseline (age 14) to Follow-up (Age 22)

Figure 5.
Bar Charts of Depression Symptom Score at age 22 and Demographic Variables

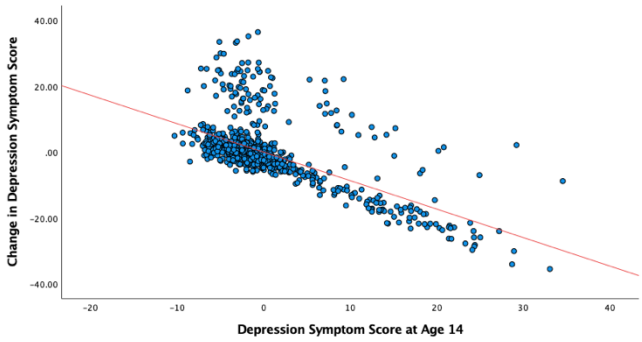


5a. Bar Chart of Change in Mean Depression Symptom Score from Baseline (age 14) to Follow-up (age 22) and Site ID
Nottingham site was significantly associated with increases in depression symptom scores. $\beta = .135$, $p < .001$
Note. ID_01: London; ID_02: Nottingham; ID_03: Dublin; ID_04: Berlin; ID_05: Hamburg: ID_06: Mannheim; ID_07: Paris
Error bars represent ± 1 standard error

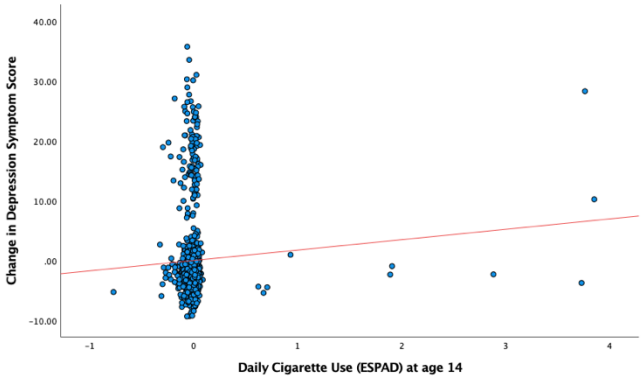


5b. Bar Chart of Change in Mean Depression Symptom Score from Baseline (age 14) to Follow-up (age 22) and Gender
Male participants showed significantly greater reductions in depression symptom scores from age 14 to age 22: $\beta = -.077$, $p = .002$
Note.
Error bars represent ± 1 standard error

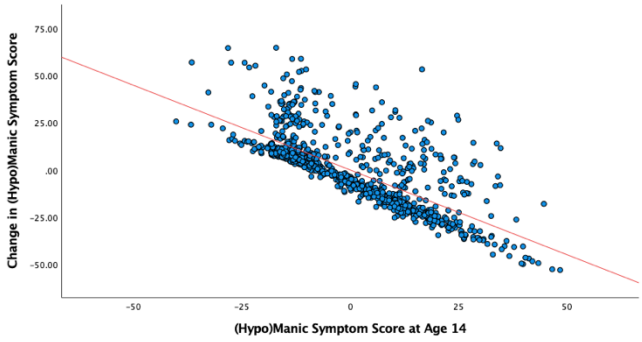
Figure 6.
Partial Regression Plots of Change in Mean Depression Symptom Score from Baseline (age 14) to Follow-up (age 22) and Clinical Variables at age 14



6a Partial Regression Plot of Change in Depression Score from age 14 to 22and Depression Score at 14
Higher levels of depressive symptoms at age 14 were significantly associated with increases in depression symptom score at age 22
$\beta = .049$, $p < .001$



6b Partial Regression Plot of Change in Depression Score from age 14 to 22, and Daily Cigarette Use at age 14
Smoking more cigarettes per day at age 14 was significantly associated with increases in depression symptom score age 22
$\beta = .051$, $p = .046$



6c Partial Regression Plot of Change in (Hypo)Manic Score from age 14 to 22and (Hypo)Manic Score at 14
Higher levels of (hypo)manic symptoms at age 14 were significantly associated with decreases in (hypo)manic symptom score at age 22
$\beta = -.754$, $p < .001$

Appendix H: Results of Longitudinal Analyses Excluding Participants Currently Taking Psychotropic Medication

Table 2.
Results of Hierarchical Regression Analyses for the Reward-Related Activations of the Bilateral Ventral Striatum at age 14 and the Depression and (Hypo)Manic Symptom Score at age 22, Excluding Participants Currently Taking Psychotropic Medication (*n* = 968)

	DV Depression Symptoms (Age 22)			DV (Hypo)manic Symptoms (Age 22)		
	β	*t*	*p*	β	*t*	*p*
Step 1: Reward-related VS activation (Age 14)						
Left-VS	-.089	-1.797	.073	.045	.916	.360
Right-VS	.002	.034	.973	-.095	-1.926	.054
	R^2 = .008, $F_{2, 965}$ = 3.736 ***p* = .024***			R^2 = .005, $F_{2, 965}$ = 2.217, *p* = .109		
Step 2: Demographics						
Left-VS	-.065	-1.327	.185	.035	.701	.484
Right-VS	-.014	-.283	.777	-.092	-1.940	.053
Age	.055	1.655	.098	.038	1.120	.262
SES	-.011	-.347	.729	-.004	-.116	.908
Gender	-.107	-3.392	**<.001*****	-.011	-.353	.724
ID_01	.089	2.080	**.038***	-.081	-1.860	.063
ID_02	.178	4.150	**<.001*****	-.042	-.959	.338
ID_03	.060	1.505	.133	-.057	-1.404	.161
ID_04	.046	1.085	.278	-.013	-.302	.763
ID_05	.048	1.131	.258	-.026	-.596	.551
ID_06	.023	.576	.565	-.013	-.304	.761
ID_07	-.007	-.156	.876	-.036	-.830	.406
	R^2 = .053, $F_{10, 955}$ = 4.552 ***p* = <.001*****			R^2 = .011, $F_{10, 955}$ = .673, *p* = .823		
Step 3: Baseline factors						
Left-VS	-.064	-1.314	.189	.037	.737	.461
Right-VS	-.012	-.245	.806	-.094	-1.933	.054
Age	.055	1.658	.098	.039	1.142	.254
SES	-.007	-.230	.818	-.004	-.117	.907
Gender	-.106	-3.340	**<.001*****	-.010	-.317	.751
ID_01	.084	1.953	.051	-.084	-1.903	.057
ID_02	.172	3.984	**<.001*****	-.049	-1.101	.271
ID_03	.048	1.184	.237	-.061	-1.477	.140
ID_04	.032	.754	.451	-.019	-.425	.671

ID_05	.043	1.004	.316	-.029	-.661	.509
ID_06	.019	.475	.635	-.015	-.353	.724
ID_07	-.012	-.278	.781	-.043	-.978	.329
Intelligence Estimate	-.022	-.673	.501	.021	.630	.529
Novelty-Seeking	.023	.705	.481	.052	1.532	.126
Monthly Alcohol Use	.002	.069	.945	-.017	-.478	.633
Daily Cigarette Use	.063	1.950	.051	-.011	-.323	.747
Lifetime Drug Use	-.008	-.219	.827	.053	1.526	.127
	R^2 = .058, $F_{5, 950}$ = 1.047 p = .388			R^2 = .016, $F_{5, 950}$ = 1.107, p = .355		
Step 4: Baseline Mood Symptoms						
Left-VS	-.056	-1.148	.251	.049	.978	.328
Right-VS	-.013	-.275	.783	-.101	-2.074	**.038***
Age	.056	1.721	.086	.040	1.186	.236
SES	-.009	-.297	.767	-.008	-.240	.810
Gender	-.096	-3.043	**.002****	-.002	-.052	.959
ID_01	.081	1.907	.057	-.080	-1.830	.068
ID_02	.167	3.905	**<.001*****	-.041	-.946	.344
ID_03	.047	1.180	.238	-.059	-1.437	.151
ID_04	.033	.785	.433	-.019	-.436	.663
ID_05	.045	1.079	.281	-.027	-.627	.532
ID_06	.019	.469	.639	-.016	-.389	.698
ID_07	-.011	-.273	.785	-.035	-.822	.411
Intelligence Estimate	-.024	-.745	.457	.021	.644	.520
Novelty-Seeking	.014	.439	.661	.040	1.204	.229
Monthly Alcohol Use	-.011	-.332	.740	-.026	-.732	.247
Daily Cigarette Use	.063	1.968	**.049***	-.008	-.2236	.814
Lifetime Drug Use	-.018	-.523	.601	.040	1.160	.464
Baseline Depression	.135	4.089	**<.001*****	.053	1.583	.114
Baseline (Hypo)manic	.059	1.775	.076	.125	3.683	**<.001*****
	R^2 = .083, $F_{2, 948}$ = 13.075 **p = <.001*****			R^2 = .038, $F_{2, 948}$ = 10.560, **p < .001*****		

Note. All reported β estimates are standardized regression coefficients. n = 968
New variables added in each step of model building are bolding to aid the reader.
ID_01: London; ID_02: Nottingham; ID_03: Dublin; ID_04: Berlin; ID_05: Hamburg: ID_06: Mannheim; ID_07: Paris
The VS activation was from the contrast of large-win vs. no-win.
VS, ventral striatum
* p < .05
** p < .01
*** p < .001
Significant findings are bolded to aid the reader.