Investigating psychobiological mechanisms underlying dysregulated goal-pursuit across psychiatric disorders

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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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Date: 02/07/2021

Overview

This thesis examines the psychobiological mechanisms contributing to dysregulated reward processing differences in two parts: across psychiatric disorders (Part one), and in bipolar disorder (Part two).

Part one comprises a systematic review and meta-analysis examining the extent to which four aspects of reward processing, namely the *anticipation* and *evaluation* of *rewards* and *losses*, exist transdiagnostically at the psychobiological level. 26 functional magnetic resonance imaging (fMRI) studies that examined whole-brain-based activation during a reward task (monetary incentive delay) and compared between patients and matched controls were included. Results showed that compared to controls, clinical groups exhibit shared increases and decreases in dorsal striatal activity during the evaluation of rewarding outcomes and anticipation of negative outcomes respectively.

Part two presents an empirical study, which sought to combine computational modelling and fMRI data to investigate whether momentary changes in mood bias the perception of rewards more strongly in individuals with bipolar disorder than matched controls. Region-of-interest analyses in the ventral striatum, anterior insula and ventromedial prefrontal cortex and exploratory whole-brain analyses were conducted. Although results broadly confirmed previous findings that mood-biased influences on reward learning signals are represented in the reward system, preliminary evidence suggests that individuals with bipolar disorder represent them more strongly than controls in visual processing areas.

Part three comprises a critical appraisal of the research process. This includes a discussion of the author's influences on the research, the relevance of understanding mechanisms in psychological research and treatment and potential challenges of fMRI research, concluding with a summary of recommendations.

Impact Statement

The present research has a number of key implications for academic research and clinical practice.

In academic research, the results from the meta-analysis of functional magnetic resonance imaging (fMRI) studies using a well-validated reward task represent an important step towards identifying shared psychobiological processes underlying dysregulated goal-pursuit and reward processing across psychiatric disorders. This study is the first whole-brain meta-analysis that examines the shared patterns of brain activation during the anticipation and outcome of monetary rewards and losses across multiple psychiatric disorders. The meta-analytic findings indicate preliminary evidence for specific transdiagnostic facets of motivational processing during the perception of rewards and the anticipation of potential losses. These findings hopefully contribute to the body of research into transdiagnostic processes underlying psychopathology rather than relying on traditional symptom-based approaches.

The findings from the empirical study represent an important step towards empirically testing an existing computational model of mood, which makes predictions about the recursive relationship between momentary mood fluctuations and perception of reward. The empirical study used fMRI to examine the extent to which mood-biased influences on reward learning signals are represented in the reward system in a clinical sample of individuals with bipolar. The current study provides preliminary evidence that compared to controls, momentary mood biases the perception of outcomes more strongly in individuals with bipolar disorder, and this tendency is generally higher in individuals with greater mood (manic and depressive) symptoms. The presence of stronger mood biases is proposed to generate unrealistic expectations of future outcomes, thereby resulting in dysregulated goal-directed behaviour. As our study used a cross-sectional design, our findings prompt further

longitudinal research to examine whether this neuro-computational model can account for exacerbations in mood symptoms in bipolar disorder.

The findings of the fMRI meta-analysis add to the wider literature highlighting a potential role for transdiagnostic interventions and call for future studies to look at whether these shared processes are amenable to intervention. Upon further replication, the findings from the empirical study may hold implications for interventions for bipolar disorder, such as those that focus on supporting top-down regulation of escalating expectations or beliefs and modulating reward-driven attentional processes, such as mindfulness, which has been shown to regulate reward-related neural responses. Overall, identifying psychobiological mechanisms underpinning dysregulated goal-pursuit and mood instability is a step forward towards making existing clinical interventions more mechanism-focused and hopefully more effective.

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Part 1: Literature Review

Reward processing as a transdiagnostic mechanism across psychiatric disorders: A coordinate-based fMRI meta-analysis of the monetary incentive delay task

Abstract

Background. Despite evidence that psychiatric disorders show high comorbidity and common mechanisms, psychiatric research predominantly examines these mechanisms within diagnostic categories. Increasing evidence suggests that dysregulated goal-pursuit and reward processing may be shared processes across disorders; however, the extent to which they share psychobiological commonalities is unclear.

Objective. We sought to establish the extent to which four aspects of reward processing are shared across disorders at the psychobiological level; namely anticipation and evaluation of outcomes; both in the reward and loss domain.

Data source. Systematic review and meta-analysis of PubMed and Web of Science databases.

Study selection. Selected studies quantified whole-brain fMRI activation during the monetary incentive delay task and compared between patients and controls.

Data extraction and synthesis. Coordinates with the following task contrasts: reward anticipation, reward outcome, loss anticipation and loss outcome, and corresponding effect sizes of brain activation were retrieved for analysis using Seed-based d Mapping.

Results. 26 studies (28 experiments) were included, comprising a total of 619 patients and 578 controls across 7 disorders (depression: n=9; bipolar disorder: n=6; schizophrenia: n=6; obsessive-compulsive disorder: n=3; eating disorder: n=3, post-traumatic stress disorder: n=1; borderline personality disorder: n=1). Compared to controls, clinical groups exhibited increased right putamen activation during reward outcome and decreased right temporal

pole, left caudate and right cerebellum (lobule VI) activation, during loss anticipation. No group differences were found for reward anticipation and loss outcome.

Conclusions. We find preliminary evidence that could suggest the presence of specific transdiagnostic facets of reward processing across disorders in relation to the evaluation of rewards and motivational salience to losses.

1. Introduction

1.1 Transdiagnostic Approaches to Psychological Treatment and Research

Existing psychological treatments and research are largely geared towards treating and understanding psychiatric disorders with the assumption that diagnoses hold causal explanatory value, although increasing evidence suggests otherwise (Maung, 2016). This diagnosis-driven focus has led to the development of an evidence-base for various diagnosis-specific treatment approaches (Pilling et al., 2011). Nevertheless, these interventions are not always effective for everyone (Andrews et al., 2004). Moreover, clinical presentations rarely fit the criteria of an uncomplicated, singular diagnosis; often comorbidity, which is likely overlooked in diagnosis-specific interventions, is the norm (Jacobi et al., 2014).

To date, research has yet to identify symptoms, biological markers or cognitive processes uniquely linked to a psychiatric disorder (Venigalla et al., 2017). Therefore, returning to research focusing on mechanisms (Holmes et al., 2018; Insel et al., 2010), could contribute to the improvement of existing interventions and the development of novel treatments that better target processes of change and have broad utility to address comorbidities and differential treatment response (Dalgleish et al., 2020).

There has been success in isolating shared (or transdiagnostic) processes, such as attentional and negative thinking biases, which manifest across non-clinical and clinical populations (Harvey et al., 2015; Mansell et al., 2008). This has facilitated the development of mechanism-informed interventions (Schaeuffele et al., 2021) such as those targeting selective attention (MacLeod & Clarke, 2015), perfectionism (Egan et al., 2011) and rumination (Watkins, 2016), among others. However, these largely focus on cognitive processes, which evidence suggests are influenced by changes in affect (e.g. during

stressful situations) and motivation (e.g. in the presence of reinforcers or punishers (Pessoa, 2009).

1.1.1 Dysregulated goal-pursuit – a potential transdiagnostic mechanism

Recently, researchers have identified reward processing, which encompasses reward- and punishment-based learning, decision-making, and goal-pursuit (Berridge & Robinson, 2003), as an affective-motivational process implicated across psychiatric disorders (Zald & Treadway, 2017). Rewards are defined as stimuli that possess value to organisms and are likely to elicit feelings of pleasure and approach behaviour (Schultz, 2007). The ability to seek rewards and avoid punishment thus facilitates optimal decision-making and goal-pursuit, which are posited to be impacted across psychiatric disorders including mood and anxiety disorders, schizophrenia, substance use disorders and non-substance addiction behaviours (e.g. problematic gambling). Specifically, decreased goal-directed behaviour (e.g. amotivation and anhedonia) is reported in depression and schizophrenia (Griffiths et al., 2014), whereas increased goal-directed and reward-seeking behaviour despite negative consequences are common features in mania, substance use disorders and non-substance addiction behaviours (American Psychiatric Association, 2013). Additionally, the avoidance of feared stimuli, which may interfere with goal-pursuit, is implicated across anxiety disorders (Dickson & MacLeod, 2004). It is therefore argued that key symptoms specified as diagnostic criteria across disorders can be explained by an overarching reward processing framework.

Advances in functional neuroimaging, particularly functional magnetic resonance imaging (fMRI), have facilitated the study of brain regions underlying cognitive and affective processes such as reward processing, which occur rapidly at an unconscious level, and cannot be quantified from behaviour or accessed via verbal report. FMRI is also a more objective measure than a questionnaire; it indirectly measures neural activity resulting from

changes in haemodynamic signals while an individual performs a cognitive task, thereby providing insights into how rewards are represented in the brain and how that is linked to differences in decision-making and goal-directed behaviour (Wang et al., 2016).

The focus of this chapter is to investigate shared neural responses to rewards and punishments across psychiatric disorders through a meta-analytic review of fMRI studies of a well-validated reward processing task (i.e. monetary incentive delay task, MIDT). An overview will be provided of key brain regions implicated in reward processing, two key components of reward processing and the MIDT, followed by a review of MIDT fMRI studies and current gaps in the literature, before the aims and hypotheses of the meta-analysis are presented.

1.2 Neurobiological Circuits Underpinning Reward Processing

The brain circuits closely linked to reward processing include dopaminergic neurons in the midbrain that project to the ventral striatum, and other interconnected limbic (e.g. amygdala) and cortical areas (e.g. orbitofrontal, ventromedial prefrontal, anterior cingulate and insula cortices) (Berridge & Kringelbach, 2015). The ventral striatum is the central hub of this network; it responds to cues signalling potential rewards and losses (Carter et al., 2009), and its activity scales proportionately with increases in reward probability and magnitude (Knutson et al., 2001; Knutson & Greer, 2008; Yacubian et al., 2006).

A large body of neuroimaging studies indicates that the striatum, orbitofrontal and ventromedial prefrontal cortices are activated by different rewards (e.g. food, art, money) (Pessiglione & Delgado, 2015). The orbitofrontal and ventromedial prefrontal cortices have been associated with computing the subjective value of stimuli (e.g. money vs. beautiful artwork), thereby guiding decision-making in the face of multiple options (Levy & Glimcher, 2012). Information about value representations is sent to the cingulate and premotor

cortices, enabling the evaluation and selection of appropriate actions to obtain rewards and avoid negative outcomes (Rolls, 2019).

The striatum also projects to the amygdala and insula, which are implicated in affective and attentional processes. The amygdala is a limbic region involved in detecting salience (i.e. whether something captures one's attention), which is central to learning about potential threats and rewards (Haber & Knutson, 2010). The insula plays an important role in interoception, which refers to attention towards bodily and affective states (e.g. hunger, urges) and studies suggest that it generates embodied representations of rewarding and punishing outcomes (Damasio, 2004; Paulus & Stewart, 2014).

The insula, together with the anterior cingulate cortex, is part of a large-scale network of brain regions (i.e. salience network) that coordinate attentional processes and mediate interactions between "reflexive" limbic regions that drive automatic behavioural responses and "reflective" frontal cortical circuits involved in cognitive control (Menon & Uddin, 2010). Ineffective coordination between these two circuits may bias decision-making towards bottom-up, reward- or threat-driven signals, and away from top-down cognitive processes required to exert behavioural control, thereby generating suboptimal behavioural responses. Investigating differences in the interactions between "reflexive" versus "reflective" networks would facilitate greater understanding of mechanisms underlying suboptimal decision-making and goal-pursuit seen across psychiatric disorders, which could inform clinical intervention.

Converging fMRI evidence suggests that imbalances in top-down frontal cortical and bottom-up circuits involved in reward and interoception are shared mechanisms underlying certain symptoms observed across psychiatric disorders. For instance, reduced regulation of the ventral striatum by the dorsolateral prefrontal cortex is proposed to underpin impulsive and risky decision-making seen in bipolar disorder and substance use disorders, whereas

the reverse pattern has been suggested in depression (Mason et al., 2014; Pujara & Koenigs, 2014; Yamamoto et al., 2015). Similarly, excessive 'top-down' prefrontal control over 'bottom-up' circuits has been proposed to underlie restrictive eating patterns and poor awareness of bodily signals related to food and hunger in eating disorders (Park et al., 2014). Taken together, these findings bring us closer to identifying shared neural mechanisms that could be targeted, across disorders, in clinical interventions.

1.3 The Anticipation and Outcome of Monetary Rewards and Losses

1.3.1 The incentive-salience model

The incentive-salience model (Berridge, 1996) posits that reward processing involves two dissociable psychological components that are not always conscious processes: "wanting" and "liking", which are mediated by different neural systems. "Wanting" refers to the motivational, attention-grabbing aspect of rewards and their learned associated cues (i.e. incentive salience), whereas the latter refers to the pleasure experienced during the outcome of reward (Berridge, 2012).

From this perspective, the enjoyment one experiences from consuming a reward may not necessarily generate the motivation to obtain it. The distinction between "wanting" and "liking" is consistent with recent conceptualisations of anhedonia, a symptom of depression and schizophrenia, which differentiates between a loss of motivation versus pleasure in response to previously rewarding activities (Treadway & Zald, 2011).

1.3.2 Monetary Incentive Delay Task (MIDT)

Many cognitive tasks used to assess neural activity during reward processing are divided into two distinct temporal components corresponding to processes of "wanting" and

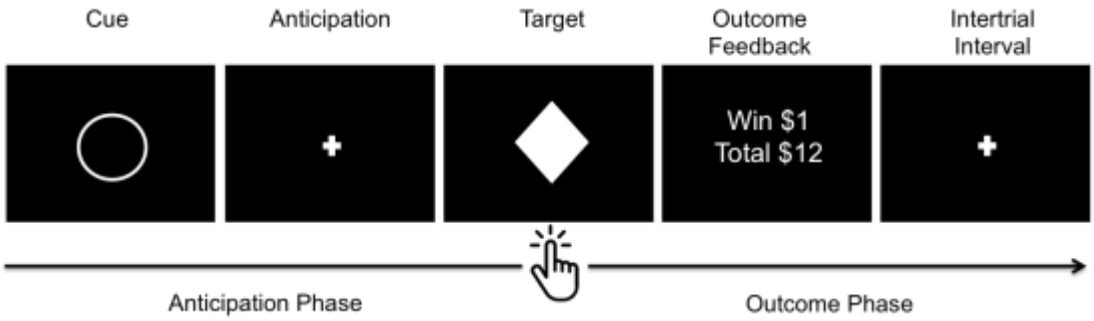
“liking”: anticipation (i.e. neural responses to cues that predict reward or loss), and outcome, (i.e. neural responses during the outcome or omission of a reward or loss).

A large body of research on reward processing in healthy and clinical populations has focused on monetary reward and loss. The MIDT (Knutson et al., 2000), a reward processing task that isolates monetary anticipation and outcome of rewards and losses into distinct temporal phases, has been well-validated and extensively used in fMRI studies - the search term “Monetary Incentive Delay” yields more than 500 studies.

The task includes different learned cues as predictors of reward or loss (e.g. circle-monetary gain, square-monetary loss, triangle-neutral i.e. no gain or loss) and a target cue, which when presented, requires a motor response. The task comprises three sequential events: anticipation cue, target presentation and outcome feedback (Figure 1). During anticipation, a cue denoting the probability of reward is presented. Following a delay in which a fixation cross is presented, the target cue is presented, which requires the participant to make the same response in each trial by pressing a button within a time window. The participant gains or avoids losing money if their response is within the time window, but fails to gain and loses the money if the response exceeds the time allotted. The time window within which participants are required to respond is constantly adjusted to achieve a successful target rate of approximately 60-66%. During outcome, feedback indicating a monetary gain, loss or neutral outcome is provided based on one’s performance (i.e. target hit or miss), followed by another delay before the start of the next trial. The timings for each phase vary across studies.

Figure 1

Schematic diagram of the MIDT



The MIDT has a low cognitive demand compared to other reward tasks (e.g. guessing tasks) in which participants are unaware of which cues predict greater reward probability at the start and have to learn based on the feedback they receive. These types of tasks examine reward-based learning that occurs when the actual outcome received is better or worse than what was expected. This mismatch results in a prediction error, which drives learning and future expectations about reward-related cues and the outcomes they predict (Schultz, 2016). However, in the MIDT, cues and their predictive outcomes are learned beforehand, typically through practice sessions, in which the task is calibrated to each individual's average response times, thereby minimising learning effects and group differences in reaction times (Balodis & Potenza, 2015).

Using the MIDT in conjunction with fMRI facilitates the isolation of neural processes recruited during the anticipation and outcome (or "wanting" vs. "liking") of rewards and losses from reward-related learning (e.g. prediction error). Investigating these reward processing components and their underlying neural bases across non-clinical and clinical populations could foster greater understanding of the mechanisms underlying the development and maintenance psychiatric disorders, which could serve as a target in clinical interventions.

1.4 FMRI Studies of the MIDT in Healthy and Clinical Populations

Several recent meta-analyses have synthesised fMRI studies using the MIDT to characterise neural activity underlying reward and loss processing during anticipation and outcome in healthy populations. For instance, Wilson and colleagues (2018) found that anticipation of monetary reward and loss activated the striatum, anterior cingulate, anterior insula and other cortical regions involved in cognitive control. Additionally, monetary reward and loss have been shown to recruit overlapping and dissociable neural regions. Oldham and colleagues' (2018) meta-analysis found that both reward and loss anticipation engage a common network including the striatum, amygdala, insula and thalamus, whereas reward outcome additionally engages the orbitofrontal and ventromedial prefrontal regions, which may reflect value representations of rewards received. Dugré and colleagues' (2018) meta-analysis on loss processing found robust activations in the anterior cingulate cortex, insula, amygdala and striatum during loss anticipation and outcome, in which ventral and lateral prefrontal regions are activated during loss anticipation and medial prefrontal regions are activated during loss outcome.

Clinical neuroimaging studies using the MIDT have identified differences in neural responses during monetary anticipation and outcome in individuals with various psychiatric disorders compared to control participants, although studies have large focused on reward and not loss processing. Decreased striatal activation to reward in depression has been a well-established finding (Arrondo et al., 2015; Pizzagalli et al., 2009; Smoski et al., 2011), supporting the theory that individuals with depression exhibit reward hyposensitivity (Alloy et al., 2016). However, inconsistencies have been reported about whether other regions (e.g. anterior cingulate cortex) show increased (Dichter et al., 2012) or decreased reward-related activation (Pizzagalli et al., 2009; Smoski et al., 2011). Similarly, while bipolar disorder has been associated with reward hypersensitivity (Alloy et al., 2016), findings from task-fMRI studies have been mixed with regards to whether ventral striatal and orbitofrontal activity are

increased (Bermpohl et al., 2010; Dutra et al., 2015) or decreased (Johnson et al., 2019; Schreiter et al., 2016; Yip et al., 2015) during monetary reward anticipation. FMRI studies investigating reward anticipation in schizophrenia have also reported conflicting results of decreased (Juckel et al., 2006), increased (Li et al., 2018; Subramaniam et al., 2015) or comparable striatal activity relative to healthy controls (Stepien et al., 2018)

Such conflicting findings could be attributed to methodological heterogeneities in fMRI protocols, MIDT design, medication and disorder subtypes (e.g. bipolar disorder I or II) and severity between studies. Moreover, depressive symptoms have been reported across psychiatric disorders (Hägele et al., 2015), which could additionally cloud the findings. Hägele and colleagues (2015) found that higher levels of self-reported depressive symptoms were associated with decreased ventral striatal activation during reward anticipation across multiple disorders including major depression, attention deficit hyperactivity disorder, alcohol use disorder and schizophrenia. This finding has been replicated in other studies of individuals with chronic pain (Kim et al., 2020), schizophrenia (Arrondo et al., 2015) and bipolar disorder (Satterthwaite et al., 2015). This suggests that the presence of depressive symptoms, regardless of whether it is a primary feature of a diagnosis, could dampen reward and loss processing activity.

These inconsistencies in the literature in relation to task heterogeneity and the confounding effects of depressive symptoms across disorders can be addressed using a meta-analysis. Heterogeneous reward tasks and stimuli (e.g. non-monetary stimuli such as social rewards) may systematically confound findings in the literature; different task types require different cognitive demands, thereby potentially engage different patterns of brain activity (Balodis & Potenza, 2015; Lutz & Widmer, 2014). Thus, conducting a meta-analysis that includes fMRI studies that use the same reward task to identify patterns of shared activation implicated across psychiatric disorders during reward processing, could mitigate such task-specific confounding effects (e.g. Oldham et al., 2018; Wilson et al., 2018). Meta-

regressions could also investigate potential effects of clinical variables such as depressive symptoms across different disorders. Given that several fMRI meta-analyses of the MIDT have examined shared patterns of neural activity in monetary reward and loss processing in healthy individuals, there is a need to do the same in clinical populations. This is especially relevant as multiple disorders share similar symptoms in which individuals' motivation, goal-pursuit and decision-making are impacted, all of which could be explained by differences in reward processing.

Existing fMRI meta-analyses of reward processing have largely focused on a single disorder. These diagnosis-specific meta-analyses have found that, on an aggregate level, striatal activations are decreased in individuals with depression, schizophrenia and substance use disorders though the findings are equivocal with some finding this reduction during reward anticipation (Chase et al., 2018; Leroy et al., 2020; Luijten et al., 2017; Radua et al., 2015; Zhang et al., 2013), whilst others found reduced activation during outcome (Keren et al., 2018; Radua et al., 2015; Zhang et al., 2013). One meta-analysis collapsed reward anticipation and outcome into one phase, which precluded the ability to localise striatal deactivation to either reward anticipation or outcome (Ng et al., 2019). Moreover, these reviews did not report conclusive results on loss processing across psychiatric disorders, potentially because some studies excluded or did not report on loss anticipation or outcome trials. In addition, further heterogeneity in these meta-analyses comes from the inclusion of studies using monetary and non-monetary reward and loss stimuli (e.g. performance feedback) (Chase et al., 2018; Leroy et al., 2020; Ng et al., 2019). Those that focused specifically on monetary rewards included studies using different tasks (e.g. instrumental reward, gambling and decision-making tasks) (Keren et al., 2018; Luijten et al., 2017; Radua et al., 2015), making it difficult to infer which processes are implicated.

1.5 Aims and Hypotheses

As highlighted, the neural mechanisms underlying reward processing have been relatively well-characterised in different psychiatric disorders, but the question of whether these constitute transdiagnostic mechanisms has so far been limited to qualitative comparisons of studies. Additionally, there are key gaps in the extant literature to be addressed. First, the aforementioned meta-analyses have only focused on a single psychiatric disorder or on healthy populations and largely focused on reward rather than loss processing; to our knowledge, there has yet to be any fMRI meta-analysis of monetary reward and loss processing that includes multiple psychiatric disorders. Additionally, previous diagnosis-specific meta-analyses on reward processing included studies using different task stimuli and paradigms, which precluded the ability to make conclusive inferences regarding the specific processes that are implicated. Given the inconsistent findings across the task-fMRI literature on monetary reward processing, there is a need to reduce sources of variability. One way to do this would be to synthesise findings from studies using the same task (e.g. MIDT). Moreover, given previous evidence that depressive symptoms were negatively correlated with striatal activation across disorders, it is important to examine the effect of depressive symptoms in driving the findings of any differences in activation between clinical and control groups.

This study aims to address the abovementioned key gaps. We performed a coordinate-based meta-analysis to identify convergence of findings from MIDT fMRI studies comparing individuals with psychiatric disorders with healthy controls. Coordinate-based meta-analyses test for consistent activation of brain regions across studies; they extract the brain coordinates and effect sizes of activation peaks of clusters of statistically significant voxels reported in fMRI studies and summarise these results. Our study aims to investigate the extent to which disruptions of neural activity underlying monetary reward and loss processing, is a transdiagnostic feature across psychiatric disorders. We also explored the extent to which depressive symptoms across disorders, as measured by self-report

questionnaires, are associated with neural activity during monetary reward and loss processing.

In line with previous diagnosis-specific meta-analyses, we expect that individuals with psychiatric disorders would show decreased striatal activations compared to healthy controls; though it is unclear from the literature whether this should be manifest during anticipation (Chase et al., 2018; Leroy et al., 2020; Luijten et al., 2017) or outcome of rewards (Keren et al., 2018) or across both (Radua et al., 2015). Additionally, we predicted that, across disorders, higher levels of depressive symptoms would be associated with decreased ventral striatal activity during reward anticipation (Arrondo et al., 2015; Hägele et al., 2015; Kim et al., 2020; Satterthwaite et al., 2015).

2. Methods

2.1 Literature Search

A systematic literature search was conducted on 17/03/2021 to identify fMRI studies using the MIDT across psychiatric disorders. The following search terms were used to identify potentially eligible studies from Pubmed and Web of Science databases: (fmri) AND (monetary incentive delay) OR (fMRI AND monetary AND (reward OR incentiv* OR anticipat*)). The reference lists of recent review papers were cross-referenced to identify further relevant published studies. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to identify studies that used whole-brain analyses of task-fMRI using the MIDT to compare clinical groups diagnosed with a psychiatric disorder and healthy control groups (Appendix A). The literature search, screening, selection and data extraction was conducted by the author, with a random twenty percent of the identified studies screened for inclusion by a second reviewer. Any

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

2.2 Study inclusion

Considering the complexity and scope of the relevant literature, we chose to focus on fMRI studies using the MIDT in individuals with psychiatric disorders, excluding neurodevelopmental and substance use disorders.

We included studies that 1) were published in peer-reviewed journals, 2) involved human participants, 3) were available in the English language, 4) used fMRI in conjunction with the MIDT, 5) reported categorical group comparisons between healthy controls and individuals with psychiatric disorders, excluding neurodevelopmental and substance use disorders, 6) used standardised diagnostic criteria to determine psychiatric diagnoses, excluding nonclinical and at-risk individuals (e.g. healthy individuals with family history of psychiatric disorders) 7) reported whole-brain coverage and whole-brain group analyses, as region-of-interest and small-volume-correction analyses bias coordinate-based meta-analyses (Müller et al., 2018), 5) reported brain coordinates in a standard stereotactic space (e.g. Montreal Neurological Institute, MNI, or Talairach spaces), 8) and included at least one of the following conditions: reward anticipation, loss anticipation, reward outcome and loss outcome, whereby each condition is contrasted with neutral conditions, where money was neither gained nor lost.

We also included placebo or baseline conditions of treatment studies comparing clinical and control groups. The study with the largest sample size was included if there was sample overlap between studies. For studies reporting whole-brain and small-volume-correction analyses (e.g. Knutson et al., 2008), peaks with small-volume-correction are included if they meet the more conservative threshold used for the whole-brain analyses

(Müller et al., 2018). Studies comparing more than one clinical group of interest to healthy controls were included as independent datasets, but those comparing subtypes within a single clinical group were excluded.

2.3 Data Extraction

We extracted the number, mean age and percentage of females, of participants from both clinical and control groups, fMRI acquisition and analysis protocols, MIDT parameters, contrast type (e.g. reward vs. neutral anticipation contrast), and peak coordinates and their effect sizes. Additionally, mean scores of depressive symptoms for the clinical groups, as measured by self-report questionnaires such as the Beck Depression Inventory-II and other equivalents, were extracted. Data extraction was repeated by the author.

2.4 Data Analysis

2.4.1 Seed-based d Mapping (SDM) meta-analysis

Coordinate-based meta-analyses were conducted using SDM software (https://www.sdmproject.com/) (Radua et al., 2010). This approach identifies brain regions that show consistent activation across studies by recreating individual voxel-level maps of effect sizes and their variances of contrasts for each study based on the input of peak coordinates and their effect sizes. When statistical values other than t-values were reported (e.g. z or p-values), they were converted to t-values using the SDM web calculator (https://www.sdmproject.com/utilities/?show=Statistics). SDM converts t-values of each peak coordinate into Hedges' *g* and takes into account the sample size of studies in its calculations of within-study variance and between-study heterogeneity, such that studies with larger sample sizes and smaller variability contribute more. These estimates of effect

sizes (Hedges' *g*) and variances for each experiment were used to make forest plots to qualitatively examine whether results might be driven by particular experiments.

Unlike other coordinate-based meta-analytic approaches (e.g. Activation Likelihood Estimate), SDM offers the possibility to have positive and negative values on the same map, offsetting effects of studies that report findings of opposite directionality (i.e. increased vs. decreased activation) (Radua & Mataix-Cols, 2012). SDM has been extensively validated in previous meta-analyses (Martins et al., 2020; Wilson et al., 2018; Luijten et al., 2017; Radua et al., 2014).

In FMRI analyses, appropriate statistical thresholding is warranted to balance the need of minimising false positives versus false negatives (Lieberman & Cunningham, 2009). In this study, analyses were based on the default number of 50 permutations and an uncorrected threshold of p= .005, which has been shown to yield an optimal balance of sensitivity and specificity, with a cluster extent of 10 voxels and peak height, SDM-Z value, of 1, to further control the probability of detecting false positives (Radua et al., 2012).

Our meta-analyses examined between-group differences (psychiatric disorder vs. healthy control) in neural activity during reward anticipation, loss anticipation, reward outcome and loss outcome.

2.4.2 Meta-regression

We conducted a meta-regression analysis to assess the effects of depressive symptoms on neural activity in individuals with psychiatric disorders during each of the four contrasts. 22 out of 28 experiments reported mean depressive symptom scores of individuals with psychiatric disorders; 15 experiments used the Beck Depression Inventory as a measure of depressive symptoms, 5 used the Hamilton Depression Rating Scale and 2

used the Montgomery-Asberg Depression Scale. Mean scores were converted into one standardised scale using equipercentile linking (Furukawa et al., 2019; Leucht et al., 2018), and were used as regressors. Equipercentile linking identifies scores from different scales with equivalent percentile ranks, facilitating the mapping of scores from one scale to another (e.g. an individual scoring in the bottom 10% for one scale will be in the same percentile rank when scores are converted to a different scale) (González & Wiberg, 2017). Although equipercentile linking assumes an association between scores on different scales, which may differ in the constructs they tap, it makes fewer assumptions about the distributions of scores between scales and facilitates the comparison of measurement errors across scales. This makes this method preferable to other alternatives, such as item response theory (González & Wiberg, 2017; Gross et al., 2012).

2.4.3 Heterogeneity, jackknife and publication bias analyses

The degree of heterogeneity of the effect sizes of our findings (i.e. significant peak coordinates) across studies was evaluated using the I^2 index, which measures the percentage of between-study variation that is attributed to heterogeneity rather than chance; I^2 values of 25%, 50% and 75% reflect low, moderate and high heterogeneity respectively (Higgins & Thompson, 2002). The replicability of the results for each meta-analysis was assessed using jackknife analyses, which involves systematically repeating the meta-analyses whilst discarding one study at a time, to check the reproducibility of the results when individual studies are removed. If a brain region retains its significance in all or most of the repeated analyses, it suggests that the effect is highly replicable. Publication bias was examined using visual inspection of funnel plots and more formally using Egger's tests (Egger et al., 1997) for each peak coordinate.

3. Results

3.1 Included Studies

26 studies with 28 experiments were included, comprising 619 individuals with psychiatric disorders and 578 healthy controls, of which 43.2% were female. Of these, 27 experiments included reward anticipation contrasts, 14 were loss anticipation contrasts, 15 were reward outcome contrasts and 6 were loss anticipation contrasts (see Figure 2 for PRISMA flow diagram). The clinical groups examined included mood disorders (depression: n=9; bipolar disorder: n=6), schizophrenia (n=6), obsessive-compulsive disorder (n=3), eating disorder (n=3), post-traumatic stress disorder (n=1) and borderline personality disorder (n=1). Details of the sample characteristics and contrasts in the included studies are shown in Tables 1 and 2 respectively.

Figure 2

PRISMA flow diagram

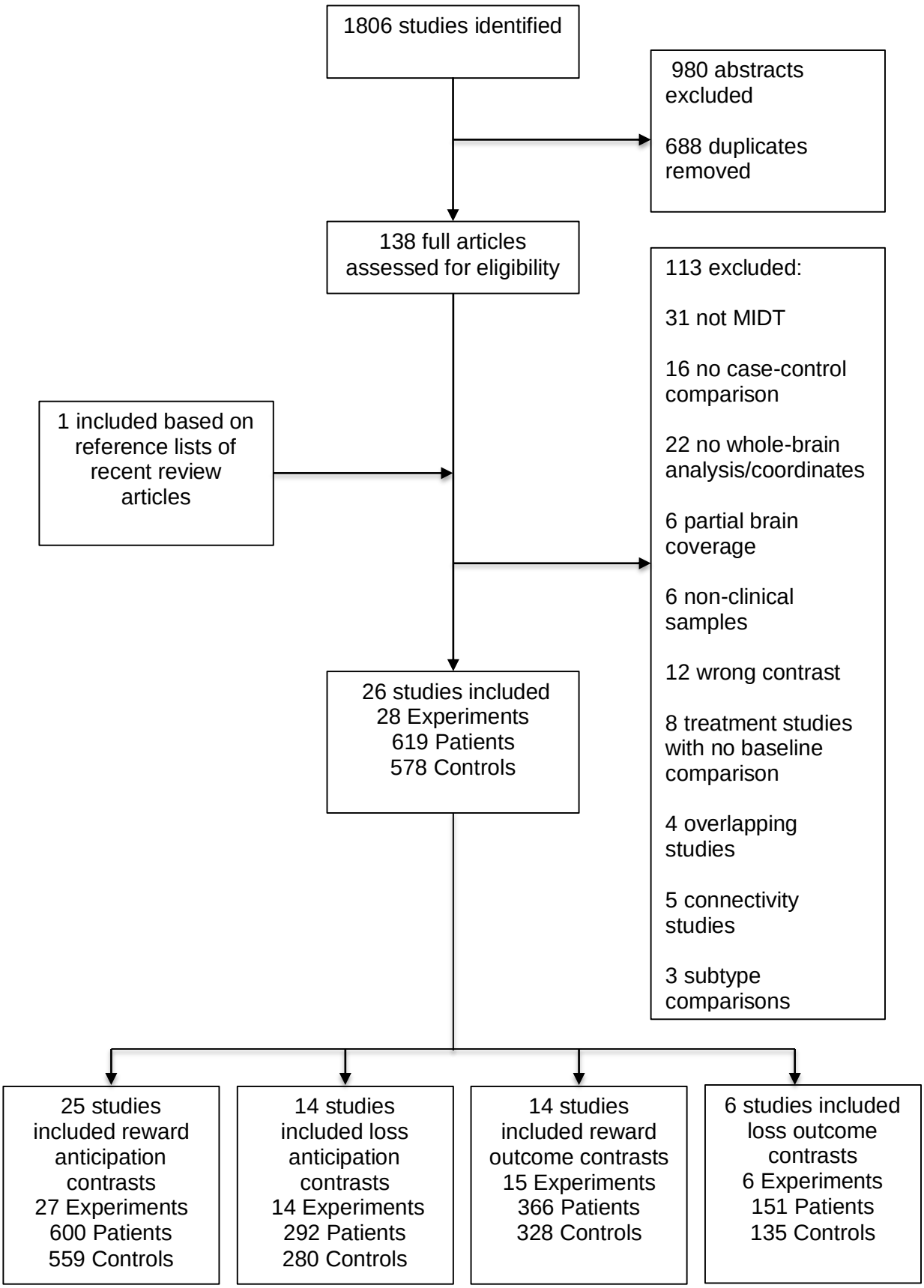


Table 1

Sample characteristics of included studies

Authors	Clinical Sample	Total *N*	Female %	Clinical Group: *n*, female (*n*), age (*M*, *SD*)			Control Group: *n*, female (*n*), age (*M*, *SD*)			Mean BDI-equivalent score
Abler et al. 2008*	Bipolar Disorder I	36	47.2	12	7	36.70 (7.80)	12	5	36.20 (11.20)	12
Abler et al. 2008*	Schizophrenia			12	5	33.90 (11.20)				13
Arrondo et al. 2015*	Major Depression	67	20.9	24	7	33.08 (9.15)	21	4	34.33 (10.11)	32
Arrondo et al. 2015*	Schizophrenia			22	3	32.73 (7.62)				20
Balodis et al. 2013	Binge Eating Disorder	38	36.8	19	14	43.70 (12.70)	19	10	34.80 (10.70)	-
Becker et al. 2017	Major Depression	40	40	20	12	43.50 (12.30)	20	9	44.90 (9.60)	28.10
Carl et al. 2016	Major Depression	53	67.9	33	22	33.20 (6.50)	20	14	31.10 (8.82)	25.27
Choi et al. 2012	Obsessive Compulsive Disorder	28	0	13	0	24.92 (6.92)	15	0	26.60 (4.29)	15.08
da Silva Alves et al. 2013	Schizophrenia (first episode)	22	0	10	0	22.70 (3.20)	12	0	34.55 (11.21)	-
DelDonno et al. 2019	Major Depression	50	80.0	23	16	25.09 (3.32)	27	23	29.15 (9.00)	30
Dichter et al. 2012	Major Depression (remitted)	38	71.1	19	15	23.60 (4.09)	19	12	27.90 (6.30)	2.63
Herbort et al. 2016	Borderline Personality	44	100	21	21	25.67 (5.98)	23	23	25.78 (5.75)	30.38

	Disorder									
Johnson et al. 2019	Bipolar Disorder I	48	47.9	24	12	37.04 (9.87)	24	11	33.92 (12.15)	4
Jung et al. 2011	Obsessive Compulsive Disorder	40	35.0	20	7	25.70 (6.99)	20	7	24.75 (3.68)	16.50
Kaufmann et al. 2013	Obsessive Compulsive Disorder	38	57.9	19	11	34.80 (11.00)	19	11	34.90 (11.80)	17
Kirschner et al. 2020	Bipolar Disorder I (remitted)	50	36.0	25	9	37.30 (9.10)	25	9	33.10 (9.70)	6
Knutson et al. 2008	Major Depression (unmedicated)	26	65.4	14	9	30.71 (8.80)	12	8	28.67 (4.25)	25.38
Li et al. 2018	Schizophrenia	52	42.3	26	11	22.77 (6.21)	26	11	24.58 (5.38)	-
Nawijn et al. 2016	Post-Traumatic Stress Disorder	72	44.4	35	14	42.49 (9.83)	37	18	41.11 (10.86)	-
Pizzagalli et al. 2009	Major Depression (unmedicated)	61	45.9	30	15	43.17 (12.98)	31	13	38.80 (14.48)	27.48
Schiller et al. 2013	Major Depression (remitted)	38	71.1	19	15	23.60 (4.10)	19	12	27.90 (6.30)	2.60
Schreiter et al. 2016	Bipolar Disorder I & II	40	60.0	20	12	41.45 (7.33)	20	12	41.60 (10.10)	2
Simon et al. 2016	Binge Eating Disorder and Bulimia Nervosa	111	-	56	-	32.66 (12.24)	55	-	31.98 (8.39)	23.96
Smoski et al. 2011	Major Depression	22	-	9	-	34.30 (15.10)	13	-	26.20 (6.30)	16.70
Stepien et al. 2018	Schizophrenia	39	35.9	16	2	32.60 (9.20)	23	12	29.50 (6.60)	9.10
Subramaniam et al. 2015	Schizophrenia	57	31.6	37	12	45.14 (9.97)	20	6	43.72 (13.32)	-
Urosevic et al. 2016	Bipolar Disorder I, II and not otherwise specified	47	38.3	21	8	16.33 (1.66)	26	10	15.90 (1.32)	-

Yip et al. 2015	Bipolar Disorder II & not otherwise specified (unmedicated)	40	45.0	20	8	22.59 (0.90)	20	10	22.10 (0.58)	12

Note. *Abler et al. (2008) and Arrondo et al. (2015) included two samples of different clinical groups, which were included as two separate experiments – the total number of participants and percentage of females are calculated to represent values for the whole study and values for the control group (i.e. number of participants, number of females and mean and standard deviations for age) are the same across experiments from the same study. "–" denotes studies that did not report data on depressive symptom scores. BDI = Beck Depression Inventory-II

Table 2

Task contrasts included in each study

Authors	Reward Anticipation	Loss Anticipation	Reward Outcome	Loss Outcome
Abler et al. 2008*	✓[a]	✗	✓[a]	✗
Abler et al. 2008*	✓[a]	✗	✓[a]	✗
Arrondo et al. 2015*	✓	✗	✗	✗
Arrondo et al. 2015*	✓	✗	✗	✗
Balodis et al. 2013	✓	✓	✓	✓
Becker et al. 2017	✓	✗	✗	✗
Carl et al. 2016	✓[a]	✗	✓[a]	✗
Choi et al. 2012	✓[a]	✓	✗	✗
da Silva Alves et al. 2013	✓	✓	✗	✗
DelDonno et al. 2019	✓	✗	✗	✗
Dichter et al. 2012	✓	✗	✓	✗
Herbort et al. 2016	✓	✓	✗	✗
Johnson et al. 2019	✓	✓[a]	✓	✗[b]
Jung et al. 2011	✓[a]	✓	✓	✗[b]
Kaufmann et al. 2013	✓[a]	✓[a]	✗	✗
Kirschner et al. 2020	✓	✗	✗	✗
Knutson et al. 2008	✓	✓[a]	✓	✗[b]
Li et al. 2018	✓	✓	✓	✓
Nawijn et al. 2016	✓[a]	✗	✓[a]	✗
Pizzagalli et al. 2009	✓	✓	✓	✓
Schiller et al. 2013	✗	✓	✗	✓
Schreiter et al. 2016	✓[a]	✓[a]	✗	✗
Simon et al. 2016	✓[a]	✗	✓[a]	✗
Smoski et al. 2011	✓	✗	✓[a]	✗
Stepien et al. 2018	✓[a]	✗	✗	✗
Subramaniam et al. 2015	✓	✓[a]	✓[a]	✓
Urosevic et al. 2016	✓	✗	✗	✗
Yip et al. 2015	✓[a]	✓[a]	✓[a]	✓[a]

Note. *Abler et al. (2008) and Arrondo et al. (2015) included two samples of different clinical groups, which were included as two separate experiments.
[a]Statistically non-significant finding. [b]Loss outcome contrasts were reported but not included because they were the wrong contrast type.

3.2 Meta-Analysis

3.2.1 Reward anticipation and outcome

There were no statistically significant between-group differences in brain activation during reward anticipation. During reward outcome individuals with psychiatric disorders exhibit increased activation in a cluster including the right putamen compared to healthy controls (Table 3, Figure 3).

Table 3

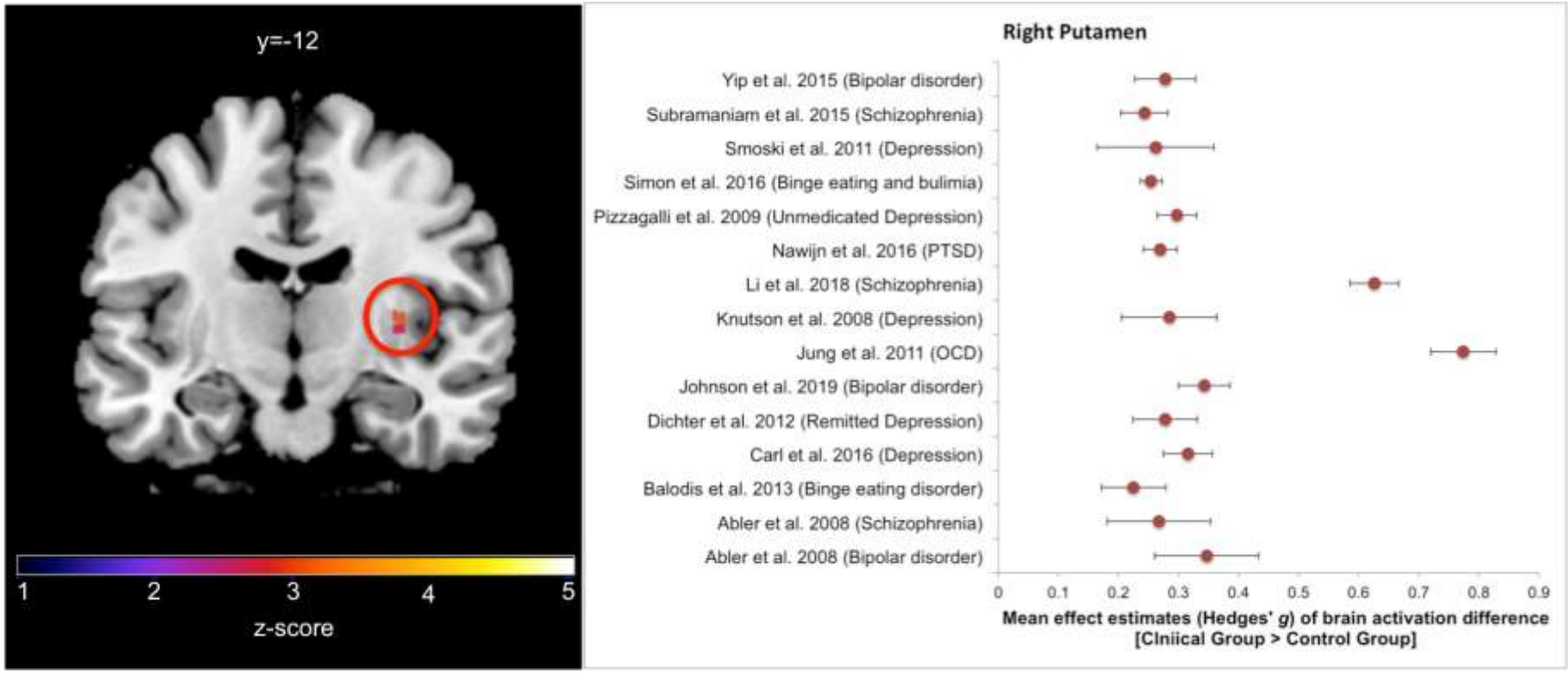
Reward anticipation and outcome meta-analysis results

Coordinates	Regions in cluster	Voxels	SDM-Z	*p*-value	I^2 (%)	Jackknife	Egger test (*p*-value)
Reward anticipation							
No significant between-group differences							
Reward outcome (Clinical>Control group)							
34,-12,6	Right putamen	36	3.068	.001	2.71*	13/15	.826
Reward outcome (Control>Clinical group)							
No significant between-group differences							

Note. *Heterogeneity (I^2) results were statistically non-significant (p>.05)

Figure 3

Increased right putamen activation in clinical groups compared to control groups and forest plot of the mean ± variance of effect sizes for activation differences in the right putamen during reward outcome



Note. Visual inspection of forest plot indicates that the two studies with the largest effect sizes (Jung et al., 2011; Li et al., 2018) might be driving the effects. All the studies show effects in the same direction.

3.2.2 Loss anticipation and outcome

During loss anticipation, individuals with psychiatric disorders exhibit decreased activation in three clusters including the right temporal pole, left caudate and right cerebellum compared to healthy controls (Table 4, Figure 4). There were no statistically significant between-group differences in brain activation during loss outcome.

Table 4

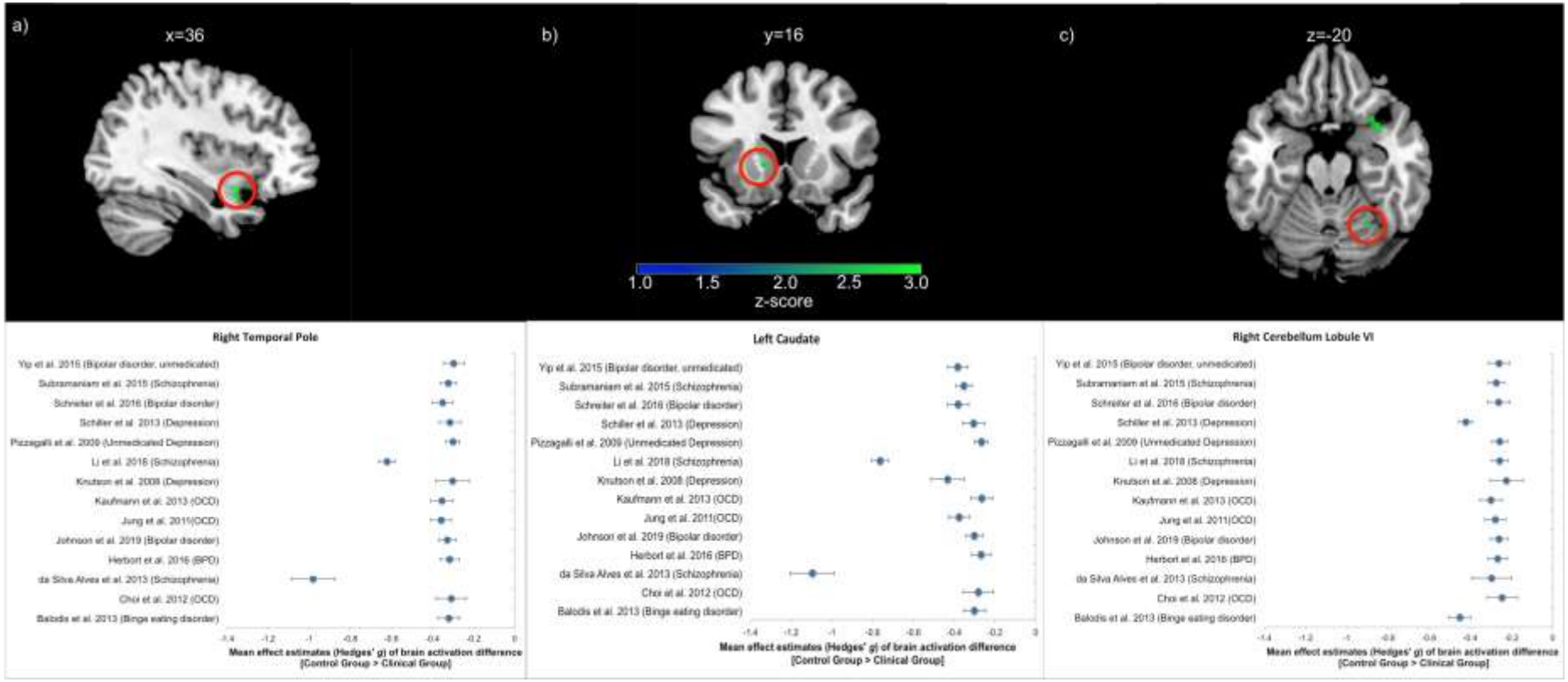
Loss anticipation and outcome meta-analysis results

Coordinates	Regions in cluster	Voxels	SDM-Z	*p*-value	I^2 (%)	Jackknife	Egger test (*p*-value)
Loss anticipation (Clinical>Control group)							
No significant between-group differences							
Loss anticipation (Control>Clinical group)							
36,6,-18	Right temporal pole, superior temporal gyrus, Brodmann Area 38	65	-3.371	.0004	3.99*	12/14	.530
-14,16,2	Left caudate	23	-3.092	.001	15.65*	12/14	.420
28,-60,-20	Right cerebellum, hemispheric lobule, VI, Brodmann Area 37	12	-2.870	.002	.70*	8/14	.965
Loss outcome							
No significant between-group differences							

Note. *Heterogeneity (I^2) results were statistically non-significant (p>.05)

Figure 4

Regions showing decreased activation during loss anticipation in the a) right temporal pole, b) left caudate and c) right cerebellum lobule VI in clinical groups compared to control groups, and their respective forest plots



Note. a-b) Visual inspection of forest plots indicate that two studies with the largest effect sizes (da Silva Alves et al., 2013; Li et al., 2018) might be driving the effects. a-c) All of the studies show effect sizes in the same direction.

3.3 Meta-Regression

Meta-regression analysis revealed a significant association between the severity of depressive symptoms and activation in the right lingual gyrus (Brodmann Area 18) during reward outcome. Specifically, individuals with psychiatric disorders with higher levels of depressive symptom scores exhibited greater right lingual gyrus activation (MNI coordinates: 14,-58,0; voxels= 27; SDM-Z= 3.132, p< .001;), which is inconsistent with our hypothesis of dampened activation (Figure 5).

3.4 Heterogeneity, Jackknife and Publication Bias Analyses

As seen in Tables 3 and 4, heterogeneity across studies for loss anticipation and reward outcome was low and statistically non-significant. Jackknife analyses showed that the increased right putamen activation during reward outcome was highly replicable as these were preserved in 13 out of 15 combinations. However, the two combinations in which findings were not replicated correspond with the exclusion of two studies with the largest effect sizes (Figure 3). The decreased activation in the right temporal pole and left caudate during loss anticipation were also highly replicable as they remained significant in 12 out of 14 combinations. However, the two combinations in which findings were not replicated correspond with the exclusion of two studies with the largest effect sizes (Figure 4a-b). The decreased right cerebellum activation was less replicable as it was only preserved in 8 out of 14 combinations. Visual inspection of funnel plots showed no clear evidence of publication bias (Figures 6-7) and was verified by statistically non-significant Egger's tests (p≥ .40), which assess funnel plot asymmetry – an indicator of whether effect sizes are more pronounced in smaller studies (Acar et al., 2018).

Figure 5

Increased right lingual gyrus activation in clinical groups that is correlated with higher levels of depressive symptoms and scatterplot depicting positive correlation between mean effect sizes of right lingual gyrus activation and severity of depressive symptoms

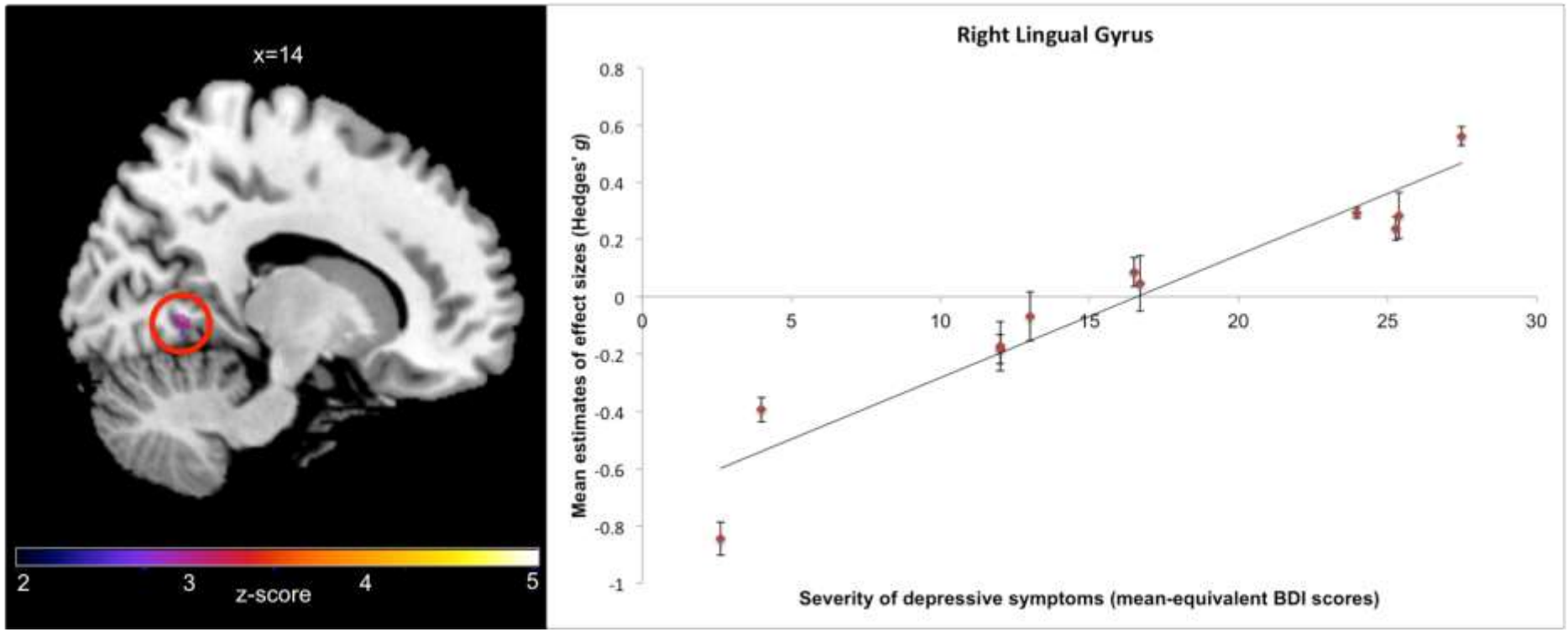
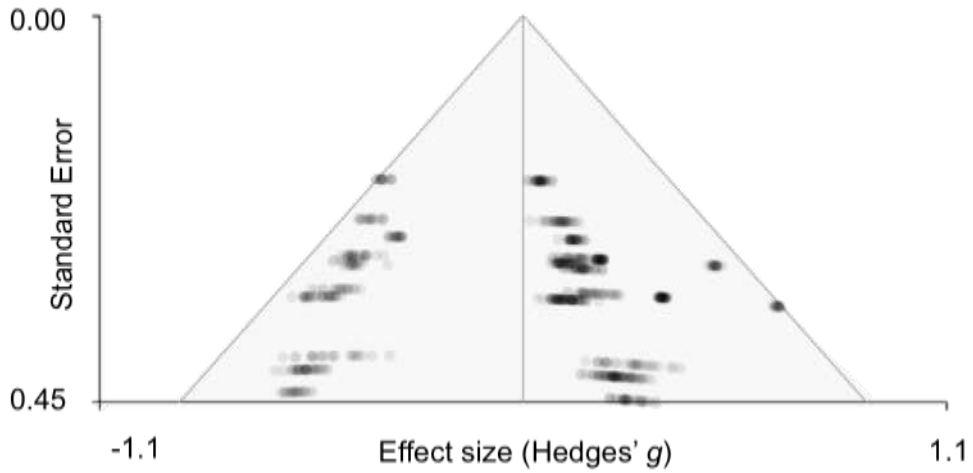


Figure 6

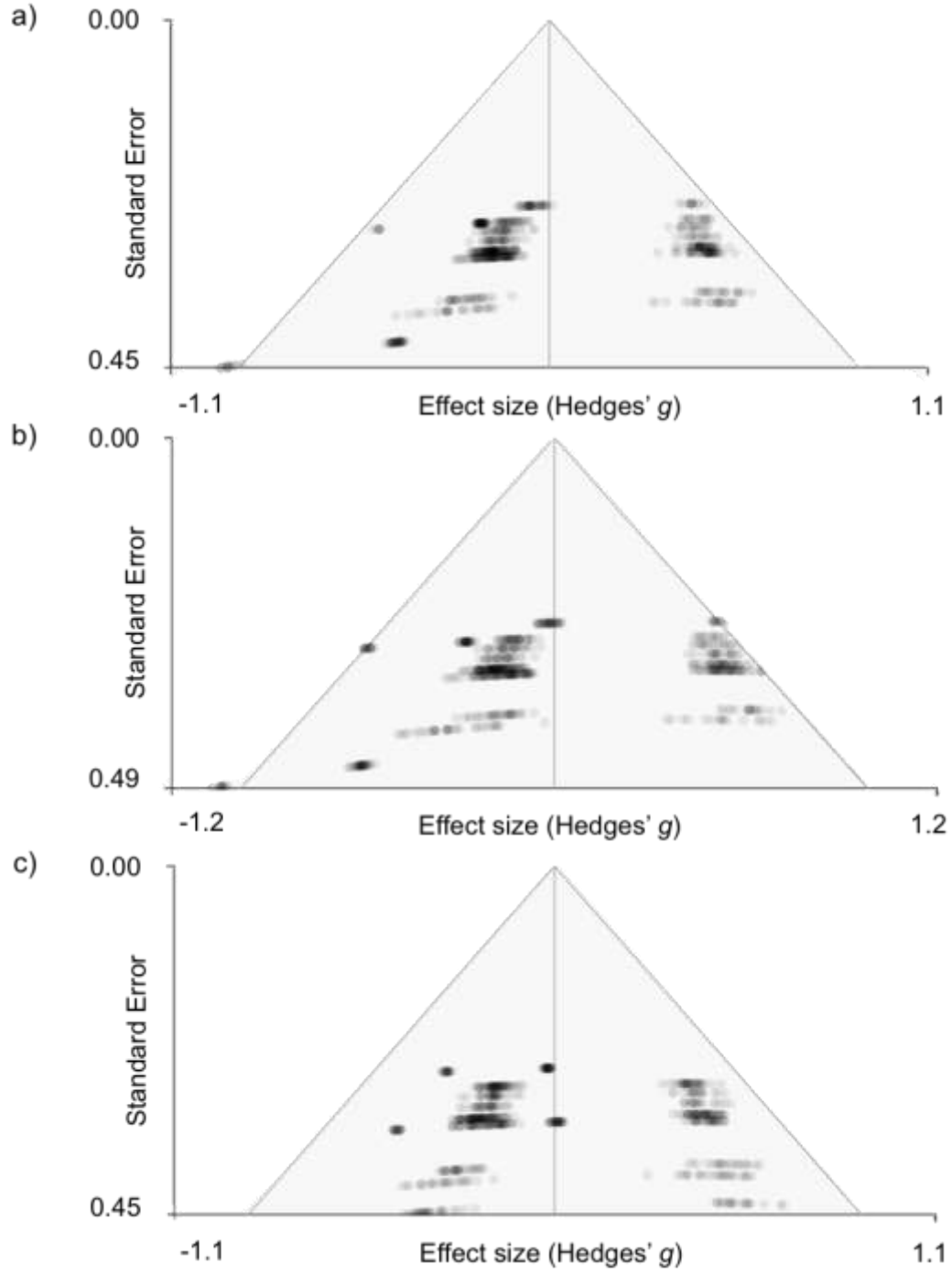
Funnel plot assessing publication bias of fMRI studies (dots) reporting group differences for reward outcome activation in the right putamen



Note. The funnel plot is approximately symmetrical with all the studies lying within the funnel, indicating no evidence of publication bias (Egger's test: p= .83).

Figure 7

Funnel plots assessing publication bias of fMRI studies (dots) reporting group differences for loss anticipation activation in the a) right temporal pole, b) left caudate and c) cerebellum lobule VI



Note. Low evidence of publication bias for right temporal pole and left caudate (95% of the studies lie within the funnel; Egger's test: p≥ .40). No evidence of publication bias for right cerebellum lobule VI as funnel plot is symmetrical with all studies lying within the funnel (Egger's test: p= .97).

4. Discussion

The current study is the first meta-analysis to directly quantify putative transdiagnostic reward- and loss-related activations, across both anticipation and outcome stages of processing. Using a coordinate-based meta-analytic approach, we found specific facets of reward- and loss-related processing that are shared across psychiatric disorders. We did not find evidence of differences during reward anticipation, but there were shared patterns of increased activity during reward outcome. During loss anticipation clinical groups exhibited decreased activity relative to healthy controls, but no significant group differences were detected during loss outcome. However, notably, follow-up jackknife analyses suggest that these findings were preserved in most but not all the iterations. This may suggest that significant findings could be due to a small set of studies, as discussed below. We also found a positive association between severity of depressive symptoms across disorders and brain activation during reward outcome.

4.1 Shared Patterns of Brain Activation During Monetary Reward Processing

4.1.1 Reward anticipation and outcome

Contrary to our predictions, our findings revealed no significant differences in brain activation between clinical and control groups during reward anticipation. Based on the incentive-salience model (Berridge, 1996), anticipation comprises a motivational component ("wanting"), whereas when the outcome is received, this elicits a hedonic component, which captures neural responses to pleasure experienced following reward outcome ("liking"). Thus, our findings suggest that motivational salience to reward, may not be a core process shared across disorders, potentially indicating the presence of categorical distinctions for this specific aspect of reward processing, which may be relevant to developing tailored clinical intervention.

Our findings differ from some of the previous diagnosis-specific meta-analyses investigating the anticipation and outcome of monetary rewards and losses, which found decreased striatal activations in clinical compared to control groups during either reward anticipation or outcome. However, some of these meta-analyses solely used a region-of-interest approach (Radua et al., 2015), which restricts findings to presupposed brain regions, and a different coordinate-based meta-analytic approach – activation likelihood estimate, which cannot incorporate studies with non-significant findings. Therefore, their findings are more susceptible to publication bias and may overestimate the effects of their findings (Müller et al., 2018). This point is exemplified by Keren and colleagues' (2018) meta-analysis that reported significant group differences in the striatum during reward anticipation between individuals with depression and healthy controls, but only when studies employing region-of-interest approaches were included.

Moreover, these meta-analyses focused on a single disorder, unlike our study, which investigated shared neural patterns across a broad range of disorders (Table 1). Notably, we used a strict whole-brain approach that incorporated studies with non-significant results and restricted analyses to a single reward task, which should address some of the methodological limitations raised in previous meta-analyses. Our null results therefore lend support to the notion that different psychiatric disorders have distinct disorder-specific neural reward processing profiles and little shared neural patterns with respect to reward anticipation. This is concordant with findings from a recent fMRI meta-analysis similarly investigating shared neural patterns, albeit across different cognitive tasks beyond reward, which demonstrated diagnostic specificity in ventral striatum activity between disorders, supported by whole-brain studies (Sprooten et al., 2017).

During reward outcome, we found that clinical groups exhibited increased activation in one cluster encompassing the right putamen, part of the dorsal striatum, which was highly replicable as effects remained significant in 13 out of 15 combinations in the jackknife

analyses. This could suggest that clinical groups show stronger responses when experiencing rewards than control groups. Notably, when the two studies on obsessive-compulsive disorder (Jung et al., 2011) and schizophrenia (Li et al., 2018) with the strongest effect sizes were left out, the findings were not replicable. However, it is clear from the forest plot (Figure 3) that the effects across all studies were in the same direction, suggesting shared differences in activation. Activity in subcortical striatal areas indicates automatic or reflexive stimulus-driven responses rather than a cognitive or reflective goal-driven process, although this activity could be up-regulated through top-down cognitive processes including attentional mechanisms. Further connectivity analyses are warranted to assess this hypothesis. Across disorders, individuals may therefore be particularly driven by bottom-up reward responses, which could be targeted in clinical interventions via top-down regulation by frontal cortical regions (Mason et al., 2016; Yang et al., 2018). Consistent with this, imbalances between bottom-up reward circuits and top-down circuits involved in cognitive control have been demonstrated across a range of disorders including eating disorders, substance use disorders, major depression and obsessive-compulsive disorder (Heo & Lee, 2018; Lipton et al., 2019; Park et al., 2014; Paulus & Stewart, 2014).

Notably, the difference in activation between clinical and control groups is localised in the dorsal rather than ventral striatum. The dorsal striatum's role in hedonic processes is unclear as previous research more consistently linked ventral striatum responses to motivation for reward and its learned cues ("wanting") and hedonic reward ("liking"). The dorsal striatum, in contrast, plays a key role in regulating movement and learning associations between actions and outcomes, which facilitates goal-directed behaviour and the automatisation of behaviour (i.e. forming habits) (Doherty et al., 2004; Everitt & Robbins, 2013).

Based on the functional dissociation between the ventral and dorsal striatum, our findings of increased dorsal striatum activation may indicate that additional processes,

beyond experiencing pleasure, are impacted. For instance, it may reflect compensatory mechanisms that support accurate planning and inhibition of motor responses during target presentation, which immediately precedes the outcome phase and thus is captured due to a spillover effect. Therefore, our findings potentially suggest that across disorders, individuals may require greater effort in inhibiting established stimulus-driven behaviours that may be suboptimal in favour of novel behavioural repertoires that support goal-directed behaviour.

Alternatively, the increased engagement of the dorsal striatum could indicate compensatory strategies in maintaining the information learned following performance feedback regarding reward-contingent actions in order to bias action selection towards rewarding outcomes (Balleine et al., 2007). Additionally, studies have shown that activation in the dorsal striatum is more prominent during tasks in which the outcome is directly contingent upon the participant's actions (Lutz & Widmer, 2014). It is important to note that although we interpreted our findings as reflecting compensatory mechanisms, we did not investigate whether clinical and control groups differed in behavioural responses (e.g. target response times). Many studies do not find or report group differences in behavioural performance. Although by design, the MIDT is typically calibrated to individual performance and response times, this does not mean that behavioural differences in reward processing are absent between clinical and control groups (Balodis & Potenza, 2015).

Taken together, upon further replication, our findings may have wider implications for clinical intervention as modulating bottom-up habit-driven responses and supporting the learning of actions and consequences could be the focus of transdiagnostic interventions. For example, recent research highlights the impact of mindfulness meditation in attenuating elevated reward-related responses in the putamen (Kirk & Montague, 2015), suggesting that the regulation of bottom-up reward-driven responses is a mechanism that is amenable to change by at least some existing clinical interventions.

4.2 Shared Patterns of Brain Activation During Monetary Loss Processing

4.2.1 Loss anticipation and outcome

In contrast to our null findings during reward anticipation, we found during loss anticipation evidence of decreased activations in the left caudate, part of the dorsal striatum, and right temporal pole, which was highly replicated in 12 out of 14 combinations in our jackknife analyses. It is important to note that when the two studies on schizophrenia with the strongest effect sizes (da Silva Alves et al., 2013; Li et al., 2018) were left out, the findings were not replicated. While this may suggest that the effects are driven by schizophrenia, findings were replicated when the one a different study on schizophrenia was left out. Additionally, the effect sizes across all the studies were in the same direction as evidenced by the forest plot (Figure 4a-b, bottom pane). There was also evidence of reduced activation in the right cerebellum lobule, though this was replicated in only 8 out of 14 combinations in our jackknife analyses. This suggests that this finding is less robust and may be driven by specific disorders (3 out of the 8 studies included schizophrenia), though all the studies showed effect sizes in the same direction (Figure 4c, bottom pane).

The decreased dorsal striatum activity could suggest that clinical groups show decreased motivational responses to avoiding losses. Though similar to our findings in reward outcome, this activation is localised to the dorsal and not ventral striatum. Hence, there may be additional processes beyond motivational salience that is implicated. While the MIDT precludes any decision-making and learning of cue-reward contingencies (Knutson & Greer, 2008), our findings could indicate that clinical groups show intact representations of loss outcomes but exhibit impairments in updating subsequent predictions of future outcomes in the dorsal striatum. Hence, these findings suggest that the shared mechanisms across psychiatric disorders are potentially related to how learning signals update future expectations of how quickly they should respond.

A previous meta-analysis of loss processing in the MIDT in a healthy population similarly reported activations in the cerebellum (lobule VI) during loss anticipation (Oldham et al., 2018). The cerebellum plays a key role in motor functions, specifically, the execution of well-timed automatic movements (Timmann et al., 2010); activation in lobule VI, in particular, has been demonstrated during simple finger movement tasks like tapping (Stoodley & Schmahmann, 2009). Thus, our findings of decreased activation in the cerebellum (lobule VI) across clinical groups potentially reflect difficulties in modulating motor control in relation to motivationally significant events, thereby failing to prioritise motor planning and action to avoid losses. Notably, lobule VI is functionally connected to the salience network – a neural circuit involved in detecting relevant information and the recruitment of other circuits to modulate behaviour (Habas et al., 2009). Hence, it could be argued that our findings suggest impairments in motivational salience towards loss stimuli. With regards to reduced activation of temporal pole, previous research has shown that this region has strong anatomical connections with the striatum and orbitofrontal cortex (Fan et al., 2014), and is involved in the integration of multisensory input and self-referential thinking (Northoff et al., 2006; Olson et al., 2007). It could be argued that decreased activation in this region reflects difficulties in integrating reward-related- and loss-related information with visuo-motor signals. Alternatively, clinical groups may be overly self-referential when trying to perform the task successfully, though this interpretation is speculative.

During loss outcome, we found no significant differences in brain activation between clinical and control groups, which seemingly indicates that clinical groups process and experience losses similarly to control groups. However, this may be due to the relatively small number of experiments that included loss outcome contrasts (n=6, with 151 patients and 135 controls) or the heterogeneity of the psychiatric disorders included, which may indicate that loss outcome involves diagnosis-specific processes. Moreover, the majority of the studies used an MIDT with a greater probability of a successful rather than a failed trial: out of the 17 studies that reported target hit rates, 15 used a probability rate of at least

greater than 60% (see Appendix B). Hence, by design these studies included fewer loss than gain trials and therefore may have less power to detect loss-related activations resulting in an under-estimations of effects related to loss processing (Ubl et al., 2015).

4.3 Severity of Depressive Symptoms and Reward-Related Brain Activation

Contrary to our expectations, we did not find an association between high levels of depressive symptoms and decreased activation in the ventral striatum across disorders during reward anticipation or outcome. This finding suggests that the presence of depressive symptoms across disorders, regardless of whether they are a primary or secondary feature of a diagnosis, do not dampen ventral striatum activity, which contrasts previous findings (Arrondo et al., 2015; Hägele et al., 2015).

Unexpectedly, we instead found a significant positive correlation between the severity of depressive symptoms and activation in the right lingual gyrus during reward outcome. Our findings seem to converge with a previous meta-analysis of reward processing in depression that reported increased lingual gyrus activity; however, this was not discussed in their main findings (Zhang et al., 2013). The lingual gyrus has been implicated in the processing and encoding of visual stimuli (Leshikar et al., 2012). Greater engagement of the lingual gyrus, in individuals with greater depressive symptoms, across disorders, could therefore indicate differences in top-down attentional processes rather than affective and hedonic processes commonly associated with ventral striatal activation. Barceló and colleagues (2000) provided evidence that prefrontal lesions modulated neural activity in visual processing areas, and therefore one could speculate that the increased lingual gyrus activity indicates compensatory mechanisms in top-down attentional modulation across clinical groups during the processing of outcomes. However, this interpretation is speculative and the role of the lingual gyrus in reward-related processing merits further study. Furthermore, only a subgroup of the experiments included measures of depressive

symptoms (reward anticipation: 21 out of 27 experiments, reward outcome: 11 out of 15 experiments, loss anticipation: 10 out of 14, loss outcome: 3 out of 6). The 6 studies that did not collect measures of depressive symptoms examined clinical populations including eating disorders, schizophrenia, bipolar disorder and post-traumatic disorder, which may slightly underestimate the effects of our findings as depressive symptoms may be present across these disorders, even if they are not considered a core feature.

4.4 Strengths and Limitations

This study has several strengths and limitations. Strengths of this current meta-analysis include focusing on a single well-validated reward task (the MIDT) to favour a homogeneous selection of fMRI studies investigating monetary anticipation and outcome. This permits greater confidence in interpreting findings of brain activation to the circumscribed number of processes involved in the MIDT, as effects would not be driven by studies using a particular task. In addition, we comprehensively examined both anticipation and outcome stages of processing and for both domains (reward and loss), as loss processing is often under reported despite its importance in optimal decision-making (e.g. weighing up the costs of potential options). We also adopted a whole-brain meta-analytic approach and excluded region-of-interest analyses and studies that reported partial brain coverage, to minimise localisation biases.

Our findings should also be interpreted within the context of several limitations present in the identification of studies, selection of a meta-analytic approach, analysis and the MIDT paradigm itself, some of which are applicable across fMRI meta-analyses. First, although an independent reviewer was involved in the process of study selection, the process of systematic literature search, data extraction, coding and analysis was conducted solely by the author, which increases the likelihood of errors. Related to this point, conducting this meta-analysis as a single researcher who had to learn the technical aspects

of using the SDM software, which was time intensive, resulted in the absence of a methodological quality assessment. Studies of low methodological quality could be a source of heterogeneity and the robustness of the findings could have been further examined by excluding lower quality studies in follow-up sensitivity analyses. Second, the current meta-analysis extracted peak coordinates that were reported in studies instead of using raw statistical brain maps, which incorporates the full image information, including effect sizes and localisation of brain activity (Radua et al., 2014). This is the norm because the latter method would require gathering raw images from the authors of the studies included in this meta-analysis, which would typically result in a large amount of missing studies.

At the level of analysis, the majority of the included studies focused only on reward processing, particularly, reward anticipation, resulting in a smaller number of experiments for the other three contrasts. Further to this, although our meta-analysis was focused on identifying transdiagnostic processes, it would have been informative to conduct confirmatory diagnosis-specific comparisons; however, there were insufficient studies for each disorder in all task contrasts ($n<10$). Additionally, the effect of some potential confounders was not examined through sensitivity and subgroup analyses due to the limited number of studies included in this meta-analysis. For instance, we collapsed across different stages of disorder severity (e.g. within- and out-of-episode), psychotropic medication use and different fMRI acquisition and analysis protocols (Appendix B). Moreover, even though the studies included here all used MIDT, they report variations in the amount of money gained or lost during reward and loss trials (Appendix C). This issue needs to be addressed in larger scale studies, which allow for sufficiently powered subgroup analyses to parse the effects of these sources of heterogeneity. However, it is important to note that the trade-off between robustness and heterogeneity is a common issue plaguing meta-analyses; having broad inclusion criteria to include more studies may increase power and reduce effects driven by single studies, but also compromise the homogeneity of the included studies (Müller et al., 2017). Furthermore, given the limited number of studies, particularly of loss

processing, and the range of psychiatric disorders included in this meta-analysis, further studies and meta-analyses of the MIDT that are sufficiently powered should be carried out to build a more consistent picture of common and dissociable neural signatures underlying the anticipation and outcome of rewards and losses across a broader range of disorders – for instance, those that are associated with differing levels of sensitivity to threat (e.g. anxiety disorders vs. psychopathy).

Finally, although the MIDT involves a simple cognitive and motor component, and is thus a good task that isolates reward processing components of anticipation and outcome, there may still be some cognitive and motor factors that could be addressed. For instance, it may be difficult to disentangle activity related to motivational processes, learning (i.e. the expectation and prediction of an outcome) and inhibitory motor responses during the anticipation stage and potentially during outcome, particularly for the latter two processes. Some studies have included a second anticipation stage following target response and prior to outcome (Balodis et al., 2013; Johnson et al., 2019) (Appendix C). Differentiating between these two anticipatory stages could disentangle learning from motivational processes as the recruitment of the latter process should be minimal following target response (Oldham et al., 2018). Additionally, future tasks using computational modelling approaches, which impose an operational and precise definition of distinct reward processing components, could provide a more nuanced insight into these shared processes across psychiatric disorders (Pessiglione et al., 2018). For instance, including trial-by-trial regressors of learning parameters may facilitate more confident interpretation of the learning processes invoked during the MIDT (Cao et al., 2019).

4.5 Conclusion

This study is the first whole-brain meta-analysis of MIDT fMRI studies that examines the shared patterns of brain activation during the anticipation and outcome of monetary rewards and losses across multiple psychiatric disorders. Overall, our findings highlight that

compared to healthy controls, individuals with psychiatric disorders exhibit shared differences in neural activity underlying the processing and hedonic experience of monetary gain and the anticipation of monetary loss. Specifically, clinical groups exhibit greater habit-driven responses to rewards and difficulties in coordinating behavioural responses and motivational salience in relation to anticipated negative consequences. Our findings suggest a lack of shared differences in neural activity across clinical groups during reward anticipation and loss outcome. Additionally, we found a relationship between the severity of depressive symptoms and heightened visual processing of rewarding outcome stimuli.

4.6 Implications for future research and clinical practice

We believe that our current findings will contribute towards identifying shared brain-based correlates to develop a more refined understanding of transdiagnostic processes underlying psychopathology rather than relying on traditional symptom-based approaches. Future clinical neuroimaging research could adopt a prospective design and examine shared neurobiological responses during the MIDT that are associated with treatment response, across disorders, following psychological interventions such as behavioural activation or cognitive behavioural therapy. This would help to identify shared mechanisms that could be more effectively and broadly targeted across psychiatric disorders, in order to address the high rates of psychiatric comorbidity and partial treatment response. Moreover, the integration of neuroimaging techniques with complementary disciplines like computational modelling may help clarify the nature of the transition from general psychiatric vulnerability to clinical levels of symptom presentation. In essence, our findings lend preliminary support to the transdiagnostic approach to mental health research; however, further replication is required in future studies to determine whether reward processing is a shared process across disorders.

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Part 2: Empirical Paper

Momentary influences of mood on reward perception in bipolar disorder: a neuro-computational fMRI investigation

Abstract

Aims. Bipolar disorder is associated with dysregulated goal-pursuit and reward responsivity, which evidence suggests is reflected at the neural level and influenced by dynamic mood fluctuations. We sought to combine computational modelling and existing functional neuroimaging data to test whether momentary mood biases the perception of rewards more strongly in individuals with bipolar disorder than healthy controls.

Methods. 42 participants (21 out-of-episode bipolar disorder patients and 21 matched controls) performed a probabilistic reward task during functional magnetic resonance imaging. An existing neuro-computational model was used to test the extent to which mood-biased expected value (EV) and reward prediction error (RPE) signals are represented in addition to standard, non-mood-biased signals in the ventral striatum, anterior insula and ventromedial prefrontal cortex (VMPFC).

Results. ROI analyses confirmed that mood-biased signals were present in ventral striatum and VMPFC, but no group differences were present. However, whole-brain analyses provide some evidence of stronger activation in visual processing areas in participants with bipolar disorder than controls. Moreover, both ROI and whole-brain analyses indicated that the representation of mood-biased signals was positively modulated by mood symptoms in the anterior insula, ventral striatum and parahippocampal gyrus and negatively modulated in default-mode regions. Participants with bipolar disorder also showed stronger tracking of standard RPE than controls in the VMPFC, and limited tracking of standard EV.

Conclusion. Our results suggest preliminary evidence that momentary mood biases the perception of outcome in individuals with bipolar disorder. We also found that while individuals with bipolar disorder track standard RPEs more intently than controls, they show limited updating of value representations, potentially maintaining unrealistic expectations about reward.

1. Introduction

1.1 Bipolar Disorder

Bipolar disorder is classically defined as a relapsing-remitting condition, which features recurrent, oscillatory mood changes that culminate in episodes of depression, mania and hypomania (a milder episode of mania in terms of symptom severity and episode duration), interspersed with periods of stable mood whilst out-of-episode (Grande et al., 2016). These mood changes are accompanied by marked behavioural changes; periods of elevated mood are typically characterised by increased goal-striving, often with damaging consequences, whereas periods of low mood are characterised by decreased motivation and pleasure in previously rewarding activities (American Psychiatric Association, 2013).

However, clinical presentations of bipolar disorder often reflect a complicated picture and accurate diagnosis remains a challenge, given the overlapping symptoms with other disorders, particularly, unipolar depression (Phillips & Kupfer, 2013). Diagnostic classifications of bipolar disorder and its subtypes use arbitrary thresholds, which are often partially fulfilled, leading to diagnoses that are “not-otherwise-specified” and have “mixed features” (i.e. co-occurring manic and depressive symptoms). Moreover, mood instability and suboptimal decision-making have been reported to persist in and out-of-episode, and across mood episodes (Adida et al., 2011; Broome et al., 2015; Swann et al., 2003), thereby challenging the fully episodic view of bipolar disorder. Critically, a significant proportion of affected individuals do not fully respond to treatments and relapses are common (Sachs & Rush, 2003). It is thus important to investigate the mechanisms underlying mood instability and dysregulated goal-directed behaviour in bipolar disorder to better inform diagnosis and intervention.

This chapter focuses on outlining existing models of bipolar disorder and current gaps that need addressing with regards to identifying a plausible psychobiological mechanism underlying bipolar disorder. Following this, the application of computational (or mathematical) modelling approaches to quantifying the relationship between mood instability and reward processing will be discussed, before outlining the present study's aims and hypotheses.

1.2 The Reward Hypersensitivity Account

Rewards are broadly categorised as stimuli that induce approach behaviours and subjective feelings of pleasure when obtained, thereby reinforcing cues and actions that promote reward attainment (Schultz, 2005). Several researchers have proposed that bipolar disorder stems from a dysregulated "behavioural activation system" – a motivational system, proposed to regulate positive affect and approach behaviour towards rewards (Alloy & Abramson, 2010; Urosević et al., 2008). This model suggests that individuals with bipolar disorder exhibit increased sensitivity to reward-related cues following successful goal-attainment or positive life events. For example, receiving a work promotion could promote increased goal-striving behaviour, energy, self-confidence and euphoria, which correspond to (hypo)manic symptoms (Urosević et al., 2008). Conversely, events that signal failures in goal-attainment (e.g. not receiving the promotion) may excessively deactivate the motivational system resulting in depressive symptoms.

However, a psychobiological mechanism that accounts for these transitions in affect and behaviour is lacking. Functional magnetic resonance imaging (fMRI) provides one objective way of studying, in real time, these multifaceted and rapid processes, which are not feasibly captured by self-report measures. Converging findings from fMRI studies of healthy populations indicate that the ventral striatum is consistently activated in response to

potential rewards and their receipt (e.g. money, food, social rewards) (Sescousse et al., 2013).

Research has suggested the presence of altered reward-related activations in bipolar disorder (Ashok et al., 2017). The behavioural activation system model predicts increases and decreases in reward sensitivity in (hypo)mania and depression respectively; however, the current fMRI evidence is mixed. For instance, several studies reported no differences in reward-related ventral striatum activity between healthy controls and individuals who were either in a bipolar manic (Abler et al., 2008; Bermpohl et al., 2010) or depressive episode (Chase et al., 2013; Satterthwaite et al., 2015). Even in individuals who are out-of-episode, it is unclear whether they exhibit increased sensitivity to rewards (i.e. reward hypersensitivity), as measured by greater ventral striatal activation (Caseras et al., 2013; Mason et al., 2014), or a dampened neural response (Schreiter et al., 2016; Yip et al., 2015). These inconsistent findings could suggest the presence of significant variations in mood within and out-of-episode (Broome et al., 2015), highlighting the need to investigate how moment-to-moment fluctuations in mood influence reward-related behaviours in bipolar disorder.

1.3 Applying Computational Modelling to the Study of Mood Instability

Computational modeling has facilitated the development of quantitative, theory-driven models to better explain empirically observed data across multiple units of analysis (Guest & Martin, 2021), placing behavioural, genetic, neurobiological and psychological measures within one mechanistic framework. Different competing models can therefore be compared against each other to more precisely infer neuro-computational mechanisms underlying mood instability in bipolar disorder.

1.3.1 Reinforcement-learning theory

Optimal learning and decision-making requires accurate representations of outcomes generated by potential choices. These representations can be operationalised through reinforcement-learning – a framework in which the difference between the expected value (EV) of a rewarding outcome and the actual outcome obtained is used to generate a learning signal referred to as the reward prediction error (RPE). This RPE signal is used to improve expectations of future outcomes (Garrison et al., 2013). In other words, when there is a discrepancy between expectations and outcomes, this 'error' is noticed, and to effectively learn from it, the brain must update future expectations, thereby guiding future behaviour. RPE signals have also been shown to impact mood (Rutledge et al., 2014); emerging evidence suggests that this relationship is bidirectional rather than one-way, as discussed in a subsequent section.

1.3.2 Neurobiological basis of EV and RPE signals

A large body of neurobiological work has linked the RPE signal to dopamine neuron activity in the midbrain and their projections to the ventral striatum. When outcomes are either better or worse than expected (i.e. positive or negative RPE), the activity of these neurons increases and decreases, respectively (Schultz, 2015). Several meta-analyses indicate that RPE signals are encoded by the ventral striatum, anterior insula and ventromedial prefrontal cortex (VMPFC) (Chase et al., 2015; D'Astolfo & Rief, 2017; Garrison et al., 2013).

The ventral striatum is a key region involved in goal-directed behaviour (Doherty et al., 2004). It responds to cues signalling potential rewards and losses (Carter et al., 2009) and its activity increases with greater reward magnitude (Knutson et al., 2001). The anterior insula is implicated in interoception – the mapping of bodily signals and affective states (Craig, 2009). It is also part of a large-scale salience network that coordinates attentional processes including the detection of salient events (Menon & Uddin, 2010). The VMPFC has

been implicated in encoding the subjective value of rewards and is posited to receive and integrate valuation signals from the ventral striatum (Hare et al., 2011; Mason et al., 2014).

Bartra and colleagues' (2013) meta-analysis demonstrated that the striatum, anterior insula and VMPFC were implicated in the subjective valuation of prospects, with the former two regions responding to both rewarding and aversive outcomes. Additionally, the estimation of EV signals during the anticipation of rewards has been shown to involve these three regions (Gläscher et al., 2009; Rolls et al., 2008; van der Meer & Redish, 2011).

1.3.3 Quantifying the relationship between mood and perception of reward

Recently, researchers have used the above reinforcement-learning framework to study the dynamic relationship between emotional states and decision-making processes. These findings suggest that violations of expectations in relation to outcomes (i.e. RPEs) drive transient mood fluctuations (Eldar & Niv, 2015; Eldar et al., 2016; Otto et al., 2016; Vinckier et al., 2018). A potential explanation of the inconsistent findings in the existing bipolar disorder fMRI literature on reward could therefore be the variability in mood occurring during experiments, both across and within participants. At the individual level, mood states are likely to fluctuate within a single experiment, in response to rewards, which in turn would bias the valuation of subsequent rewards. For instance, a string of rewarding outcomes would increase one's mood especially if better than expected (e.g. winning several bets on a roulette game), thereby increasing the value of subsequent reward outcomes, and vice-versa for a string of worse-than-expected outcomes (Eldar et al., 2016; Otto et al., 2016). In support of this, Mason and colleagues (2014) found that, out-of-episode, residual mood symptoms of mania and depression (which presumably led to differences in mood during the experiment) were associated with an up- and down-regulation of reward-related activation in the ventral striatum. Eldar and colleagues (2016) argued that these mood biases can be adaptive. For example, a level of positive mood bias may help one cope with negative

events; however, in excessive amounts, it can lead to an overly optimistic outlook, resulting in the belief that one is invulnerable to negative events.

Recent research that applied computational models to fMRI data in healthy participants has provided emerging empirical support that moment-to-moment mood fluctuations affect the perception of rewards and influence subsequent decision-making. Eldar and Niv (2015) found that healthy individuals with higher self-reported traits of mood instability valued monetary rewards differently following an event that influenced their current mood state (i.e. winning or losing a much larger sum of money on a wheel of fortune). This is exemplified by greater RPE-related activity in the striatum and VMPFC during a positive mood state (after winning $7) and vice-versa. They compared a mood-biased reinforcement-learning model, in which mood biases the perception of reward value, against non-mood-biased (standard) models, in which mood exerts no effect on reward valuation. In this mood-biased model, a mood bias parameter is included, which captures the influence of mood on perceived reward. This generates mood-biased EV and RPE signals, which may elicit further mood instability and unrealistic expectations. Mood is quantified as the accumulation of recent outcomes, which biases the perception of reward. For example, reward will be perceived as larger after a string of $7 wins (i.e. good mood) resulting in inflated RPE estimates. The results indicated that the mood-biased model better represented RPE-related activity in the striatum, outperforming the standard model.

In related work, Vinckier and colleagues (2018) found that mood fluctuations induced by positive and negative performance feedback modulated neural activity in the VMPFC and anterior insula. This in turn influenced the valuation of potential wins and losses during decision-making. Specifically, greater VMPFC activity was associated with increased risk-taking due to inflated expectations of potential wins whereas greater anterior insular activity was associated with decreased risk-taking due to inflated expectations of potential losses. Finally, Rutledge and colleagues (Rutledge et al., 2014) demonstrated that EV and RPE

signals in the striatum predict moment-to-moment positive mood in relation to outcomes during a reinforcement-learning task. Self-reported positive mood was also shown to be associated with anterior insula activity.

Drawing from this work, Mason and colleagues (2017) proposed a computational account of bipolar disorder, based on this dynamic interplay between fluctuating mood states and perception of reward. While a moderate mood bias may be adaptive and facilitate optimal learning about a changing environment, individuals with bipolar disorder may inherently have stronger mood biases. This could result in recursive cycles of marked escalations in mood, expectations and behaviour, which culminate in manic symptoms when mood is elevated. Conversely, as expectations about rewards become increasingly unrealistic, the mismatch between high expectations and actual outcomes lead to negative RPEs and a deterioration in mood, culminating in depressive symptoms. Notably, the model predicts that a strong mood bias would result not only in reward hypersensitivity (when momentary mood is elevated) but also in dampened sensitivity (when momentary mood is low), thereby offering an explanation for the conflicting empirical data on reward sensitivity in bipolar disorder discussed in an earlier section.

Taken together, recent computational fMRI studies demonstrate the two-way/bidirectional relationship between mood and reward processing (Eldar & Niv, 2015). Importantly, they provide initial evidence that mood fluctuations can modulate EV (Vinckier et al., 2018) and RPE signals (Eldar & Niv, 2015) represented in the ventral striatum, anterior insula and VMPFC. Moreover, these studies highlight the role of anterior insula activation as a neural correlate of momentary mood (Rutledge et al., 2014; Vinckier et al., 2018). However, the above studies were conducted with healthy populations, highlighting the need to examine whether findings translate to clinical populations.

1.4 Aims and Hypotheses

The present study aims to test whether momentary mood fluctuations bias the perception of outcomes in a clinical sample (i.e. individuals with bipolar disorder who are out-of-episode). We will investigate this by applying an existing mood-biased reinforcement-learning model (Eldar & Niv, 2015) to previously collected behaviour and fMRI data (Mason et al., 2014). Eldar and Niv (2015) have validated a model that formalises mood based on the accumulation of recent outcomes. We predict that this model, which allows mood to vary dynamically and bias the perception of rewards, would represent reward-related neural activity in addition to a standard model in which mood exerts no effect. Based on findings that increased tracking of mood-biased signals is associated with greater self-reported hypomanic traits (Eldar & Niv, 2015), we expect that individuals with bipolar disorder will show stronger mood biases. Additionally, we predict that individuals with bipolar disorder with higher levels of mood (manic and depressive) symptoms would show stronger mood biases as measured by greater reward-related brain activation.

Given that previous research has highlighted the important roles of the ventral striatum, anterior insula and VMPFC in representing EV and RPE signals, this study will employ a region-of-interest (ROI) approach focusing on these three regions. We also report whole-brain analyses given that two fMRI studies have examined mood's influence on reward perception, and none have characterised this in a clinical sample.

In summary, this study sought to test three hypotheses:

H1a) Mood-biased EV will be represented in the three ROIs (ventral striatum, anterior insula and VMPFC) in addition to standard EV;

H1b) Participants with bipolar disorder will show increased tracking of mood-biased EV in the three ROIs, relative to matched controls;

H2a) Mood-biased RPE will be represented in the three ROIs in addition to standard RPE; H2b) Participants with bipolar disorder will show increased tracking of mood-biased and RPE in the three ROIs, relative to matched controls,

H3a) Higher levels of manic and depressive symptoms, indicative of stronger underlying mood bias (Mason et al., 2017), will be associated with increased tracking mood-biased EV; H3b) Higher levels of manic and depressive symptoms will be associated with increased tracking mood-biased RPE.

Finally, given evidence that anterior insula represents subjective momentary mood (Rutledge et al., 2014; Vinckier et al., 2018), we examined whether activity in this region tracked model-estimated mood during outcome, the phase in which mood is updated (Rutledge et al., 2014), as a confirmatory check that the neuro-computational model fitted plausible values of mood.

2. Methods

2.1 Design

This study is a secondary analysis of behavioural and fMRI data in which adults diagnosed with bipolar disorder and healthy controls underwent fMRI scanning whilst performing a Roulette task (Mason et al., 2014). The present study extends this earlier work by applying a computational model-based approach, in which momentary changes in mood are modelled and their influence on reward-related learning signals (i.e. EV and RPE) is quantified.

2.2 Power Analysis

Power analysis was informed by Eldar and Niv (2015)'s study, which compared striatal and VMPFC activations between healthy participants exhibiting low versus high trait mood instability, as defined by median split on the Hypomanic Personality Scale (Eckblad & Chapman, 1986). Using a similar reward-based task, they found a significant difference in striatal activations between participants with high and low mood instability with an effect size of d=.90, which we used to determine the implied power in our study. We conducted a power calculation using G*power (Faul et al., 2007) and yielded 89% implied power with our sample size of 42 participants at an alpha level of .05. Given that our study examines striatal activation between a clinical sample (i.e. individuals with bipolar disorder) and healthy controls, the effect size obtained should be significantly larger than those obtained in Eldar and Niv (2015)'s sample of healthy participants.

2.3 Participants

Participants with out-of-episode bipolar disorder were recruited from specialist affective disorder clinics and local mental health trusts within Greater Manchester, United Kingdom. Healthy control participants were recruited from the general community, matched for age, sex and years of education. Informed written consent was obtained from all participants.

For inclusion in this study, participants had to be between 18 and 45 years of age, have a weekly alcohol intake below 26 units and report no substance use four months before the study. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 2005) was used to confirm the diagnosis of bipolar disorder and screen healthy control participants. Individuals who did not meet threshold for either manic or depressive episodes (i.e. out-of-episode) for two months before the study were included. None of the controls warranted further assessment on any of the SCID modules. Individuals were excluded if they had received antipsychotic medication six months before the study.

2.4 Procedure

All participants completed questionnaires before fMRI scanning and performed a Roulette Task (detailed below) during scanning.

2.4.1 Questionnaires

Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960) with possible total scores ranging from 0 to 52. Manic symptoms were assessed using the 11-item Bech-Rafaelsen Mania Scale (MAS) (Bech, 1995), with possible total scores ranging from 0 to 44.

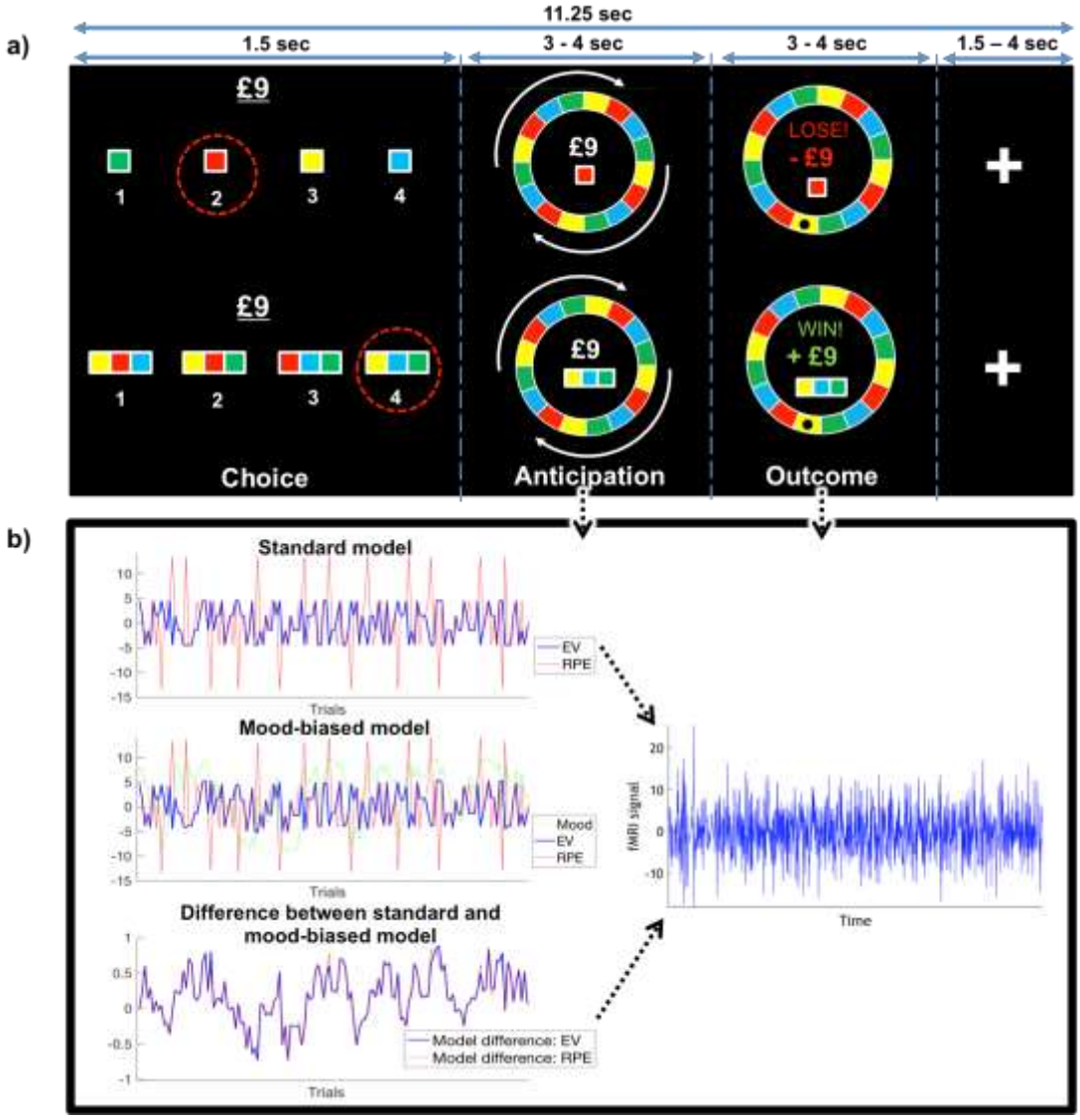
2.4.2 Roulette task

Participants completed a variant of a validated Roulette task (van Eimeren et al., 2009), in which reward probability and magnitude were independently manipulated. Each trial consists of three stages: choice, anticipation and outcome (Figure 1). During choice, participants chose between four options that confer the same probability of reward. In low probability trials (25% chance of reward), participants selected one of four individual colours that made up the Roulette wheel. In high probability trials (75% chance of reward), they selected between four sets of three colours and won if the Roulette wheel stopped on any one of the three colours. The stake on offer (reward magnitude) was also presented prior to choice, with equal numbers of low (£3) and high (£9) magnitude trials. During anticipation, the Roulette wheel spun (3-4s). At outcome, the wheel stopped spinning with the location of the Roulette ball indicating whether the participant had won or lost the amount of money shown to be at stake at the choice phase.

Participants were instructed to respond within the fixed duration of the choice phase; otherwise, a random choice would be automatically selected for that trial. They were informed that they would be paid the actual winnings following task completion. Participants completed 272 trials across eight blocks, each lasting approximately six minutes.

Figure 1

Schematic of the Roulette task and parametric regression of EV and RPE signals



Note. a) Participants placed bets on which colour would win in a Roulette spin. The trial sequence included three phases: choice, anticipation and outcome. b) Visual illustration of the regression of parametric modulators: standard and mood-biased EV and RPE signals, onto fMRI signal during anticipation and outcome. Adapted with permission from (Mason et al., 2014).

2.5 FMRI Acquisition and Preprocessing

A 1.5-Tesla Philips scanner was used to acquire eight runs of 150 volumes of functional images using an echo-planar image sequence with repetition-time = 2450ms, echo-time = 25ms, flip angle = 90°, slices = 30 in ascending order, slice thickness = 4mm, in-plane resolution = 1.5 x 1.5mm and a standard field-of-view.

Following acquisition, preprocessing of raw fMRI data is needed to account for non-neuronal signals including head motion, MRI-induced artifacts, physiological contributions and tissues outside the scope of study and minimise data variability (Caballero-Gaudes & Reynolds, 2017).

SPM12 (Wellcome Department of Cognitive Neurology, University College London) and Matlab R2018b were used to preprocess and analyse images. Each participant's functional images were motion-corrected using a six-parameter rigid-body transformation to the mean image and slice-time-corrected to the middle slice. Functional images were next co-registered with each participant's structural image, spatially normalised to the Montreal Neurological Institute (MNI) standard template and smoothed using an 8mm Gaussian kernel. Intrinsic autocorrelations were accounted for by AR(1) and low frequency drifts were removed via the 128s high pass filter. The author additionally used the ArtRepair toolbox (Mazaika et al., 2009) to minimise the impact of artifacts via the interpolation of outlier volumes.

2.6 Statistical FMRI Parametric Analyses

Individual first-level analyses were conducted using a whole-brain general linear model (GLM) as implemented in SPM12. FMRI BOLD responses in each run for each participant were modelled using regressors representing the three task conditions (Choice,

Anticipation and Outcome) and six motion-realignment parameters to reduce residual effects of motion. Additional regressors including standard and mood-biased EV and RPE estimates were calculated per trial.

On each trial, standard EVs are calculated for gain outcome (positive EV), loss outcome (negative EV), and the net of these two quantities (net EV = positive + negative EV). Net EV is calculated as the product of reward magnitude and probability (positive EV) added to the product of loss magnitude and probability (negative EV). When we refer to standard EV, we refer to standard net EV values. Standard RPE was calculated in each trial as the difference between standard EV and the actual outcome (outcome minus net EV). Mood-biased EV and RPE estimates were calculated using Eldar and Niv (2015)'s mood-biased model (Table 1). Mood is modelled as the accumulation of recent outcomes (Appendix D).

We generated standard and mood-biased EV and RPE estimates using a Matlab analysis script that implemented Eldar and Niv (2015)'s computational model. Because mood-biased learning signals are very highly correlated with standard signals, they cannot be entered into regression models due to collinearity. To solve this, mood-biased learning signals were calculated as the difference between standard and mood-biased signals. These quantities were entered as parametric modulators (i.e. regressed against neural activation on each trial) during anticipation (standard EV and mood-biased EV) and during outcome (standard RPE and mood-biased RPE). In total, the first-level GLM model included 13 regressors, which were convolved with a canonical haemodynamic response function. Individual contrast images (Choice, Anticipation, Anticipation-standard EV, Anticipation-mood-biased EV, Outcome, Outcome-standard RPE and Outcome-mood-biased RPE) were computed. Individual contrast images of interest (standard and mood-biased EV and RPE) from the first-level were passed to a second-level GLM to examine within-group and

between-group activations. These analyses produced mean statistical maps of the contrast images of interest computed at the first-level analysis for each group.

Table 1

Calculations of EV and RPE learning signals

Condition name	Probability	Magnitude	Standard positive EV	Standard negative EV	Net EV (Standard positive + negative EV)	Outcome	Standard RPE (Outcome – Net EV)	Mood-biased net EV	Mood-biased Outcome	Mood-biased RPE
Unexpected low reward	0.25	3	0.75	-2.25	-1.5	3	4.5	Net EV scaled by mood	Outcome scaled by mood	Mood-biased Outcome – mood-biased net EV
Unexpected low loss	0.25	3	.75	-2.25	-1.5	-3	-1.5	Net EV scaled by mood	Outcome scaled by mood	Mood-biased Outcome – mood-biased net EV
Unexpected high reward	0.25	9	2.25	-6.75	-4.5	9	13.5	Net EV scaled by mood	Outcome scaled by mood	Mood-biased Outcome – mood-biased net EV
Unexpected high reward	0.25	9	2.25	-6.75	-4.5	-9	4.5	Net EV scaled by mood	Outcome scaled by mood	Mood-biased Outcome – mood-biased net EV
Expected low reward	0.75	3	2.25	-0.75	1.5	3	1.5	Net EV scaled by mood	Outcome scaled by mood	Mood-biased Outcome – mood-biased net EV
Expected low loss	0.75	3	2.25	-0.75	1.5	-3	-1.5	Net EV scaled by mood	Outcome scaled by mood	Mood-biased Outcome – mood-biased net EV
Expected high reward	0.75	9	6.75	-2.25	4.5	9	4.5	Net EV scaled by mood	Outcome scaled by mood	Mood-biased Outcome – mood-biased net EV
Expected high loss	0.75	9	6.75	-2.25	4.5	-9	-4.5	Net EV scaled by mood	Outcome scaled by mood	Mood-biased Outcome – mood-biased net EV

Note. Positive EV = Probability x Magnitude; Negative EV = (1-Probability) x (-1 x Magnitude); net EV = positive EV + negative EV; RPE = Outcome – net EV; mood = model-estimated mood multiplied by a mood bias parameter of 1.2

2.6.1 ROI analyses

To examine whether anticipatory and outcome activation in the ventral striatum, anterior insula and VMPFC are parametrically modulated by standard and mood-biased EV and RPE within and between groups, we conducted ROI analyses in these regions. ROI analyses are a common approach to fMRI analysis when there are clear a-priori regional predictions of task-related activation based on prior research (Poldrack, 2007). Corrections for multiple comparisons at the whole-brain level are overly conservative when there are clear predictions; ROI analyses limit the number of statistical tests to several ROIs and control for Type I errors (Poldrack, 2007).

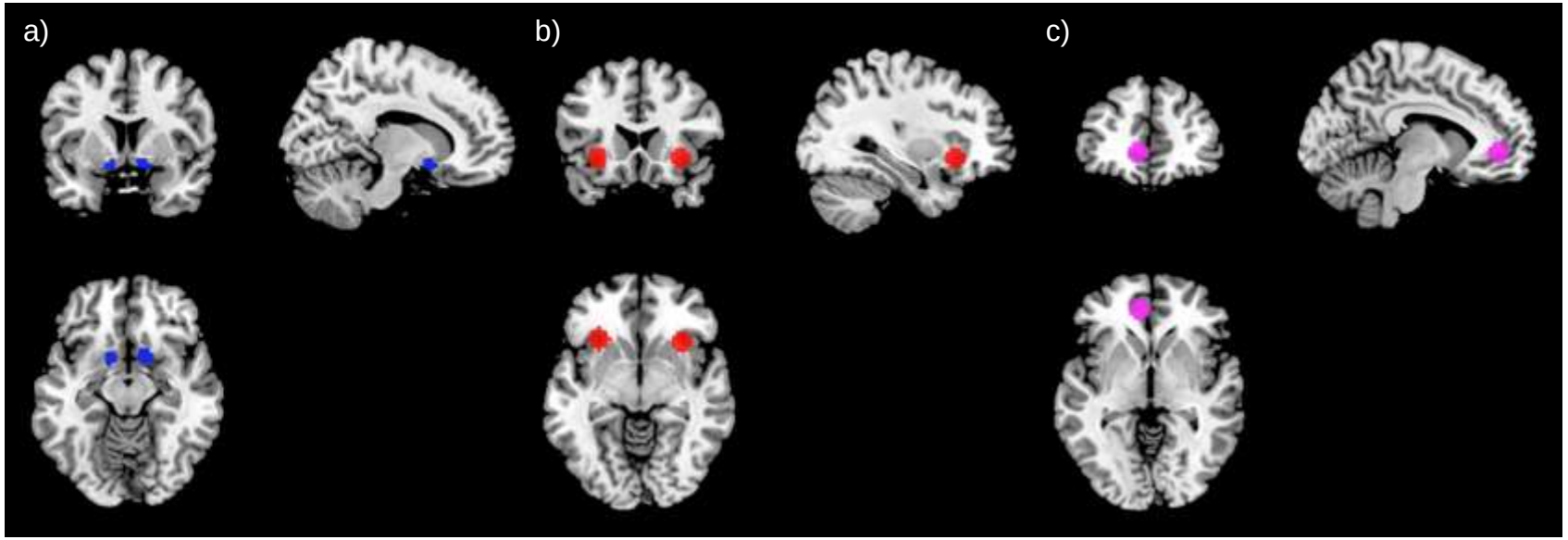
The WFU PickAtlas tool (version 3.0.5) was used to generate an anatomical bilateral ventral striatum ROI mask by selecting the left and right nucleus accumbens regions (Figure 2a). Peak coordinates for the VMPFC (x=-8, y=44, z=-2) were taken from Mason and colleagues (2014)'s study whereas peak coordinates for the bilateral anterior insula (left: x=-30, y=22, z=-6; right: x=32, y=20, z=-6) were taken from Vinckier and colleagues (2018)'s study to create ROI masks using 8mm spheres centered around peak coordinates (Figures 2b-c). The mean fMRI signal (beta estimates) across voxels in these ROIs for each participant were extracted for each contrast of interest using MarsBaR SPM toolbox (http://marsbar.sourceforge.net/) and exported to Statistical Package for the Social Sciences (SPSS) for further analyses.

One-sample *t*-tests were conducted in SPSS on brain activity during the anticipation and outcome phases in the bilateral ventral striatum, bilateral anterior insula and VMPFC separately to test whether the regression weights for EV and RPE learning signals (standard or mood-biased) are different from zero – i.e. whether the ROIs represent the learning signals above what would be expected by chance.

Repeated-measures analysis of variance (ANOVA) tests were also conducted in SPSS during the anticipation and outcome phases in the three ROIs separately. EV and RPE learning signals (standard or mood-biased) were entered as within-group factors and group (healthy control or bipolar disorder) was entered as the between-group factor. For bilateral regions (ventral striatum and anterior insula), laterality (left or right) was additionally entered as a within-group factor. The significance threshold for the repeated-measures ANOVA ROI analyses was Bonferroni-corrected for three ROIs [p= .016 (.05/3)].

Figure 2

Region-of-interest masks for a) bilateral ventral striatum, b) bilateral anterior insula, and c) VMPFC



2.6.2 Exploratory whole-brain analyses

Whole-brain within-group and between-group activations were calculated using one-sample and two-sample t-tests, respectively, with a cluster-corrected $p < .05$ family-wise error rate. This means that the significance level pertains to the likelihood that a cluster of contiguous voxels did not arise by chance. The necessary size of the cluster is denoted by the value of the cluster extent threshold (i.e. k threshold).

2.6.3 Modulation of anticipatory and outcome activation by mood symptoms

Depressive and manic symptom scores were entered as covariates in separate ROI and whole-brain analyses. These analyses only included participants with bipolar disorder because healthy controls, by design, reported very low levels of depressive and manic symptoms.

2.7 Normality and Multicollinearity Checks

To evaluate whether assumptions of normality for parametric testing were met, the normality of available continuous demographic and questionnaire data of interest (HAMD and MAS) were verified using the Shapiro-Wilk test and a skewness and kurtosis of between ±1.00 (Appendix E). Shapiro-Wilk tests were statistically significant for manic but not depressive symptom scores ($p > .05$). A log transformation was subsequently applied to manic symptom scores.

To assess multicollinearity, a Pearson's correlation was conducted between depressive and manic symptom scores of participants with bipolar disorder, yielding moderate and significant correlations between the two ($r = .60$, $p < .001$). However, we entered depressive and manic symptom scores as covariates into one rather than separate

fMRI regression models to elucidate associations between BOLD responses and mood symptoms. Entering them separately may increase the risk of Type I errors, as there is insufficient power to tease the effects of depressive and manic symptoms apart.

3. Results

3.1 Demographic Characteristics

Twenty-one participants with bipolar disorder and twenty-one healthy controls participated in this research. Participant demographic data is presented in Table 2.

An independent samples t-test and chi-square analysis indicated no significant between-group differences in age ($p = .34$) and sex ($p = .76$). As expected, participants with bipolar disorder had higher depressive ($M = 3.83$) and manic symptoms ($M = 3.55$) than controls ($M = .60$; $M = .38$) [depressive symptoms: $t(24.90) = -4.73$, $p < .001$; manic symptoms: $t(33.08) = -5.61$, $p < .001$]. T-tests for unequal variances were reported because Levene's test for homogeneity of variances was violated [depressive symptoms: $F(1,40) = 20.60$, $p < .001$; manic symptoms: $F(1,40) = 9.44$, $p = .004$].

Table 2

Participant demographics

	Bipolar disorder, n=21	Healthy controls, n=21	Statistic	*p*-value
Age, M (SD)*	35.95 (8.34)	33.25 (9.32)	*t*(38) = -.97	.34
Female, n (%)	11 (52.4%)	9 (42.9%)	χ2(1) = .38	.76
Years of education, M (SD)*	14.08 (2.47)	14.70 (2.29)	*t*(38) = .83	.41
Primary diagnosis, n				
BD-I	18			
BD-II	3			
Current comorbidity, n*				
GAD	2			
Lifetime diagnoses, n*				
AUD/SUD	10			
Panic disorder	4	1		
GAD	2			
OCD	1			
Medications, n*				
Lithium	8			
Valproate	5			
Lamotrigine	2			
SSRI	3			
SNRI	3			
Benzodiazepine	1			
z hypnotic	3			
None	4			
HAMD-17, M (SD)	3.83 (2.96)	0.6 (1.04)	*t*(24.90) = -4.73	*p*<.001
MAS-11, M (SD)	3.55 (3.09)	0.38 (1.11)	*t*(25.05) = -4.43	*p*<.001

Note. *Data from 2 participants are missing and not included. BD-I = Bipolar I Disorder; BD-II = Bipolar II Disorder; GAD = Generalised Anxiety Disorder; AUD = Alcohol Use Disorder; SUD = Substance Use Disorder; OCD = Obsessive-Compulsive Disorder; HAMD = Hamilton Depression Rating Scale; MAS = Bech-Rafaelsen Mania Score; SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin-Norepinephrine Reuptake Inhibitor

3.2 ROI Analyses

We tested whether 1) ROIs represent learning signals during anticipation (standard and mood-biased EV) and outcome (standard and mood-biased RPE) using one-sample t-tests, and 2) whether individuals with bipolar disorder track mood-biased signals more strongly than controls, using repeated-measures ANOVA. A summary of the statistical findings for one-sample t-tests and ANOVAs are presented in Tables 3 and 4 respectively.

3.2.1 Tracking of EV signals (H1a) and group differences in tracking of EV signals (H1b) during anticipation

Ventral striatum. Counter to our predictions, ventral striatum activation did not track standard EV in either group as confirmed with one-sample t-tests (Table 3, Figure 3a); additionally, ventral striatum activation tracked mood-biased EV only in healthy controls [one-sample t-test: t(20)=2.54, p= .019]. Findings from the repeated measures ANOVA revealed no significant main effects or interactions (Table 4).

Anterior insula. Similarly, anterior insula activation did not track standard or mood-biased EV in either group (Table 3, Figure 3b). No significant main effects or interactions were found, though the interaction between EV and group trended towards showing greater tracking of mood-biased than standard EV in controls and standard than mood-biased EV in participants with bipolar disorder (Table 4, Figure 3b).

VMPFC. VMPFC activation did not track mood-biased EV in either group (Table 3, Figure 3c); additionally, VMPFC activation tracked standard EV only in controls [one-sample t-test: t(20)=-2.44, p= .024]. Visual inspection of the plotted graph suggests that EV-modulated VMPFC activations are small and negative across groups (Figure 3c). No significant main effects or interactions were found (Table 4).

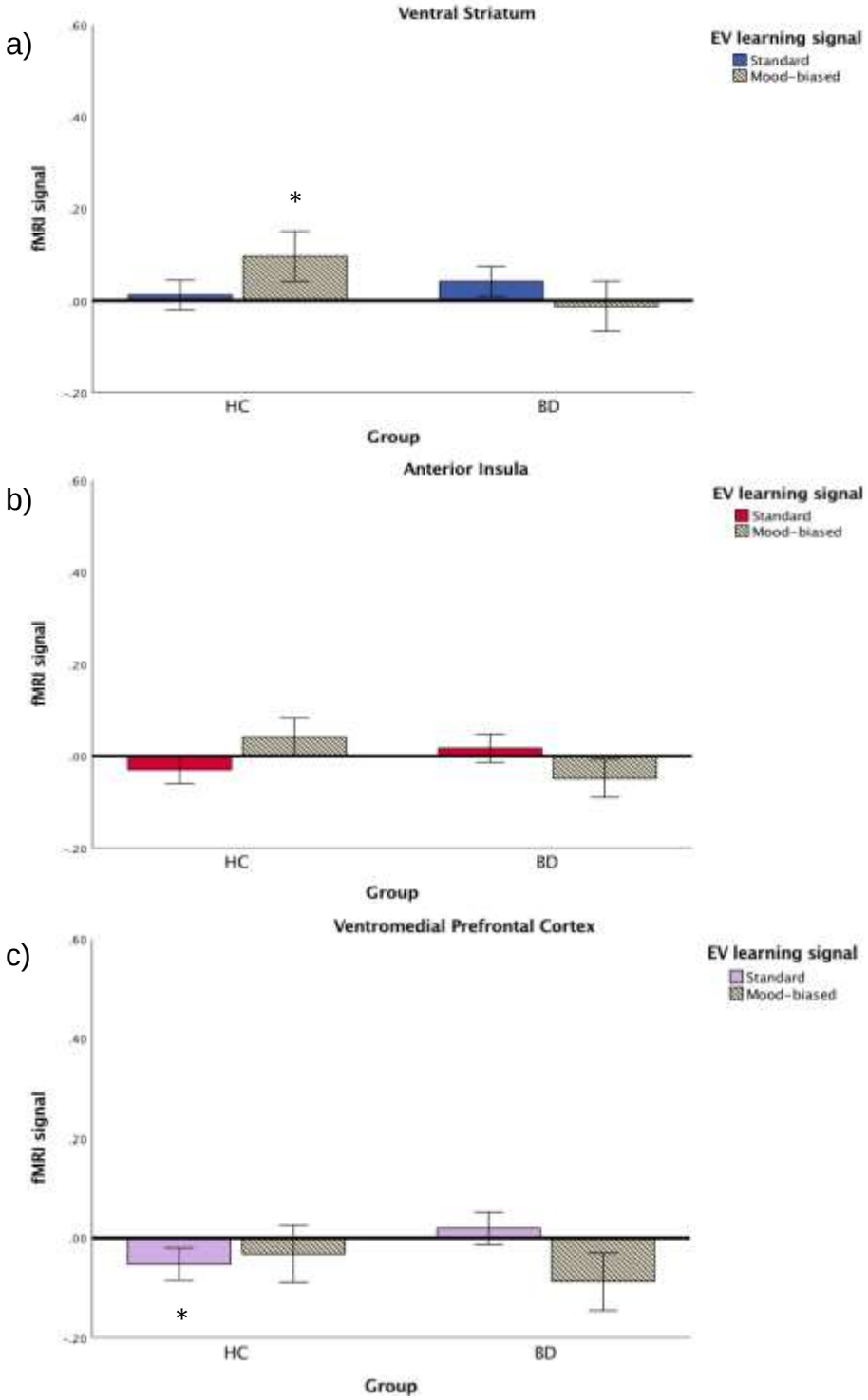
Table 3

Summary of one-sample t-tests results

	Learning signal	M	*t*	*df*	*p*
Healthy controls					
Ventral striatum	Standard EV	.12	.40	20	.697
	Mood-biased EV	.10	2.54	20	.019
	Standard RPE	.35	7.04	20	.0000001
	Mood-biased RPE	.04	.64	20	.529
Anterior insula	Standard EV	-.03	-1.33	20	.198
	Mood-biased EV	.04	.89	20	.385
	Standard RPE	.14	2.35	20	.029
	Mood-biased RPE	.06	1.00	20	.328
VMPFC	Standard EV	-.05	-2.44	20	.024
	Mood-biased EV	-.03	-.77	20	.451
	Standard RPE	.11	2.37	20	.028
	Mood-biased RPE	.12	2.05	20	.054
Bipolar disorder					
Ventral striatum	Standard EV	.04	1.18	20	.253
	Mood-biased EV	-.01	-.19	20	.853
	Standard RPE	.36	3.60	20	.002
	Mood-biased RPE	.06	.69	20	.498
Anterior insula	Standard EV	.02	.47	20	.644
	Mood-biased EV	-.05	-1.39	20	.180
	Standard RPE	.18	2.93	20	.008
	Mood-biased RPE	.05	.75	20	.46
VMPFC	Standard EV	.02	.48	20	.640
	Mood-biased EV	-.09	-1.26	20	.223
	Standard RPE	.40	3.75	20	.001
	Mood-biased RPE	.07	.72	20	.481

Figure 3

Modulation of anticipatory activity by EV: a) controls track mood-biased EV in the ventral striatum, b) neither group tracks standard and mood-biased EV in the anterior insula and c) controls track standard EV in the ventromedial prefrontal cortex



Note.
*Significant one-sample *t*-test. HC = healthy control; BD = bipolar disorder

3.2.2 Tracking of RPE signals (H2a) and group differences in tracking of RPE signals (H2b) during outcome

Ventral striatum. As expected, ventral striatum activation tracked standard RPE across groups as confirmed by one-sample t-tests [Figure 4a, controls: $t(20)=7.04$, $p< .001$; bipolar disorder: $t(20)=3.60$, $p= .002$], whereas mood-biased RPE was not tracked by either group (Table 3). The ventral striatum showed a significant main effect of RPE learning signal [$F(1,40)=11.81$, $p= .001$], but no significant interactions (Table 4).

Follow-up pairwise comparison tests indicated stronger modulation of outcome activation by standard than mood-biased RPE across groups (controls: $p= .018$, 95% CI [.06, .56]; bipolar disorder: $p= .022$, 95% CI [.05, .54]). Counter to our expectations, we did not find evidence of between-group differences in which mood-biased RPE was tracked more strongly by participants with bipolar disorder than controls ($p\geq .86$) (Figure 4a).

Anterior insula. Anterior insula activation tracked standard RPE across both groups as confirmed by one-sample t-tests [Figure 4b; controls: $t(20)=7.04$, $p< .001$; bipolar disorder: $t(20)=2.35$, $p= .029$], whereas mood-biased RPE was not tracked by either group (Table 3) (Figure 4b). However, no significant main effects or interactions were found (Table 4, $p\geq .18$).

VMPFC. VMPFC activation tracked standard RPE across both groups as confirmed by one-sample t-tests [Figure 4c; controls: $t(20)=2.37$, $p< .028$; bipolar disorder: $t(20)=3.75$, $p= .001$]. A one-sample t-test confirmed that VMPFC activation weakly tracked mood-biased RPE at trend-level only in controls [controls: $t(20)=2.05$, $p= .054$; bipolar disorder: $t(20)=-1.26$, $p= .223$]. The VMPFC showed a significant interaction between group and RPE learning signal [Figure 4c; $F(1,40)=18.23$, $p< .001$].

Follow-up pairwise comparisons indicated that standard RPE (M= .40) was tracked more strongly than mood-biased RPE (M= .07) in individuals with bipolar disorder (p= .006, 95% CI [.10, .56]). However, in controls, standard RPE (M= .11) was tracked comparably to mood-biased RPE (M= .12) (p= .915, 95% CI [-.24, .22]). We found a significant between-group difference in which standard RPE was tracked more strongly in individuals with bipolar disorder (M= .40) than controls (M= .11) (p= .018, 95% CI [.05, .52]). No significant differences in mood-biased RPE modulated activity were found between controls (M= .12) and participants with bipolar disorder (M= .07) (p= .623, 95% CI [-.17, .28]).

Table 4

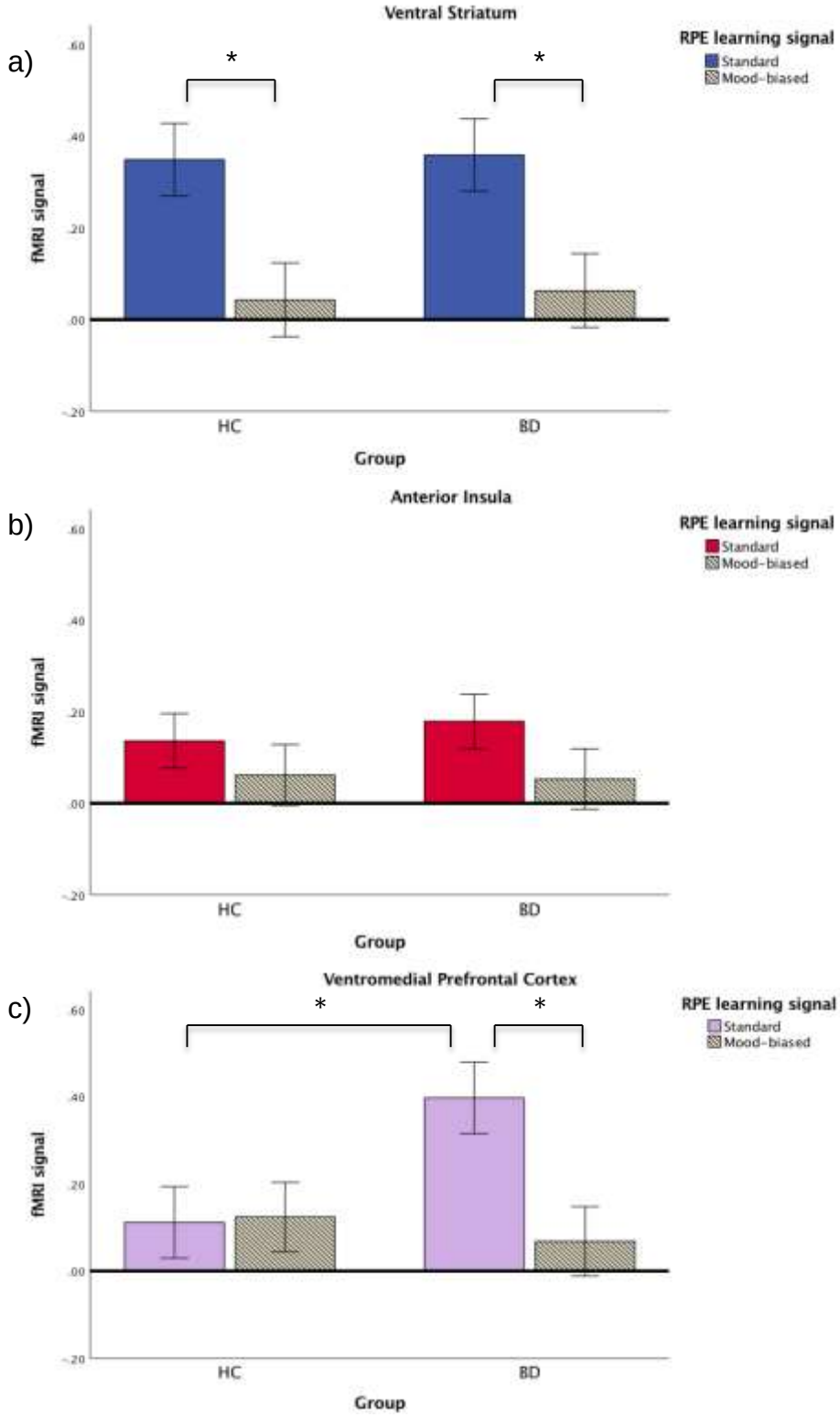
Summary of repeated measures ANOVA results

Factors	*F*	*df*	*p*
EV			
Ventral striatum			
Main effects			
Laterality	.004	1, 40	.950
EV	.12	1, 40	.734
Group	.70	1, 40	.408
Interactions			
Laterality*Group	.08	1,40	.774
EV*Group	2.58	1,40	.116
Laterality*EV	.55	1, 40	.462
Laterality*EV*Group	.002	1, 40	.965
Anterior insula			
Main effects			
Laterality	.14	1, 40	.714
EV	.004	1, 40	.950
Group	.44	1, 40	.511
Interactions			
Laterality*Group	.07	1, 40	.796
EV*Group	3.03	1, 40	.09
Laterality*EV	1.96	1, 40	.169
Laterality*EV*Group	.09	1, 40	.763
VMPFC			
Main effects			
EV	.65	1, 40	.425
Group	.04	1, 40	.839
Interactions			
EV*Group	1.42	1, 40	.241
RPE			
Ventral striatum			
Main effects			
Laterality	1.36	1, 40	.251
RPE	11.81	1, 40	.001
Group	.05	1, 40	.832
Interactions			
Laterality*Group	.006	1, 40	.938

RPE*Group	.003	1, 40	.955
Laterality*RPE	.11	1, 40	.744
Laterality*RPE*Group	.74	1, 40	.395
Anterior insula			
Main effects			
Laterality	1.22	1, 40	.277
RPE	1.9	1, 40	.176
Group	.112	1, 40	.74
Interactions			
Laterality*Group	.48	1, 40	.277
RPE*Group	.13	1, 40	.724
Laterality*RPE	.62	1, 40	.436
Laterality*RPE*Group	.002	1, 40	.963
VMPFC			
Main effects			
RPE	3.98	1, 40	.053
Group	1.96	1, 40	.169
Interactions			
RPE*Group	4.61	1, 40	.038

Figure 4

Modulation of outcome activity by RPE: a) both groups track standard RPE more strongly than mood-biased RPE in the ventral striatum, b) both groups track standard RPE, but not mood-biased RPE in the anterior insula and c) participants with bipolar disorder track standard RPE more strongly than controls in the ventromedial prefrontal cortex



Note. *Significant pairwise comparisons at $p < .05$. HC = healthy control; BD = bipolar disorder

3.3 Modulation of Anticipatory and Outcome ROI Activation by Mood Symptoms and Model-Estimated Mood

As mentioned in the Methods section, follow-up analyses of the effect of mood symptoms on EV- and RPE-modulated activity were restricted to participants with bipolar disorder as controls, by design, reported very low levels of depressive and manic symptoms. Follow-up analyses were also conducted to test whether outcome activation in the anterior insula was modulated by trial-wise model-estimated mood values.

3.3.1 H3a: Tracking of EV signals during anticipation

Anterior insula. The anterior insula showed no additional significant main effect or interactions when mood symptoms were added as covariates (Appendix F), though the main effect of depressive symptoms trended towards significance (p= .02; Bonferroni-corrected p> .016).

The ventral striatum and VMPFC showed no additional significant main effects or interactions (Appendix F).

3.3.2 H3b: Tracking of RPE signals during outcome

Anterior insula. The anterior insula showed additional significant main effect of laterality [F(1,18)=7.77, p= .012], interaction between laterality and manic symptoms [F(1,18)=7.41, p= .014] and main effect of manic symptoms [F(1,18)=7.49, p= .014] .

Follow-up pairwise comparison tests suggest no significant differences in RPE-modulated activity between left (M= .12) and right anterior insula (M= .11) (p= .72, 95% CI [-.05, .07]). Follow-up Spearman's correlations indicated that manic symptoms were

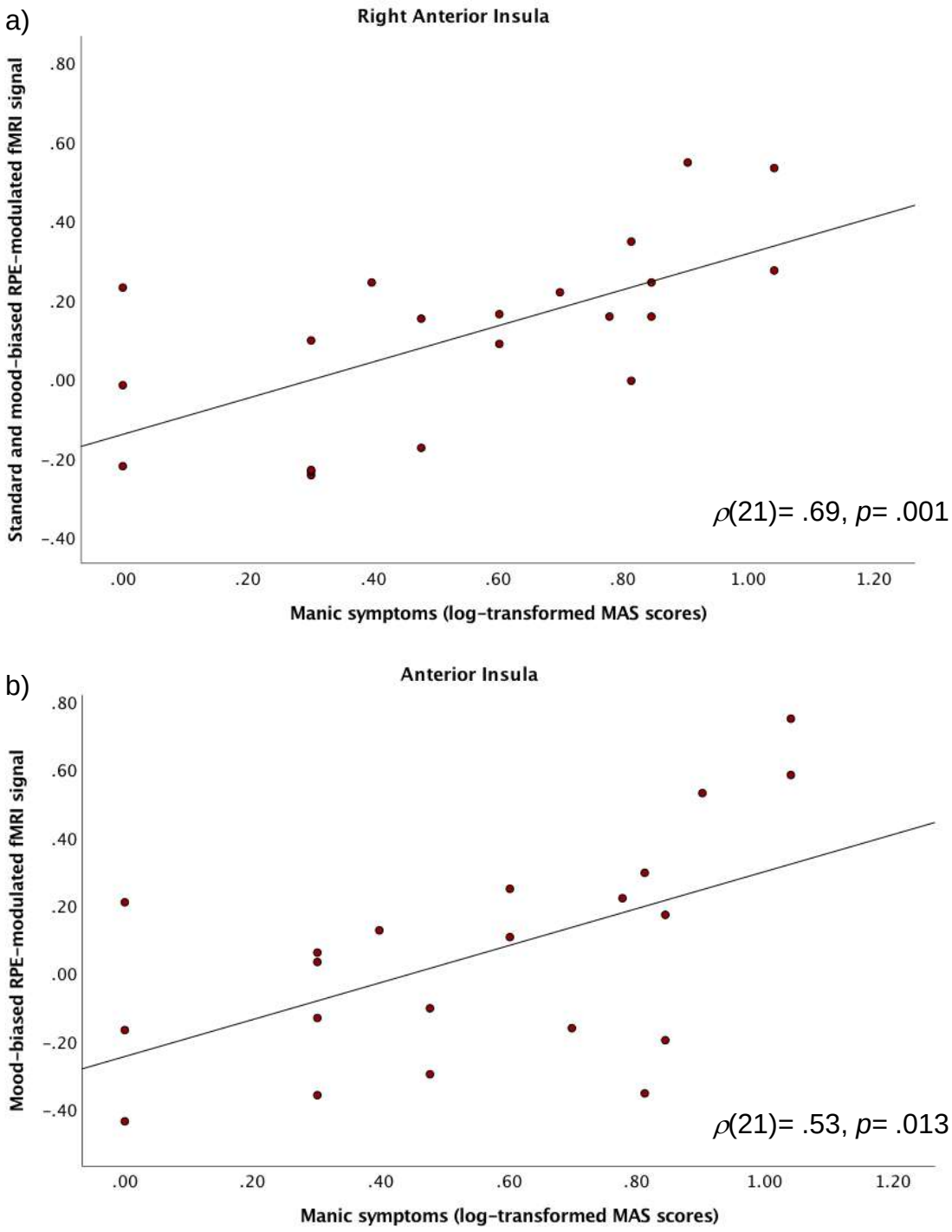
significantly correlated with right, but not left anterior insula activity modulated by the mean values of standard and mood-biased RPE added together [ρ(21)= .69, p= .001; ρ(21)= .43, p= .051] (Figure 5a). We found that manic symptoms were positively correlated with mood-biased, but not standard RPE-modulated activity in the anterior insula [ρ(21)= .53, p= .013; ρ(21)= .10, p= .668] (Figure 5b).

Follow-up analyses showed that model-estimated mood modulated right anterior insula activation in participants with bipolar disorder [one-sample t-test: M= 1.87, t(20)=2.04, p= .024], but not controls [one-sample t-test: M= .13, t(20)= .18, p= .43]. No significant group differences were found, though participants with bipolar disorder trended towards showing greater activity modulated by model-estimated mood, compared to controls [t(40)= 1.50, p= .07]. Model-estimated mood also modulated left anterior insula activation in controls [one-sample t-test: M= 1.60, t(20)=3.09, p= .002], but not in participants with bipolar disorder though the latter trended towards showing greater activation modulated by model-estimated mood [one-sample t-test: M= .93, t(20)=1.44, p= .08]. No significant group differences were found [t(40)= .81, p= .21].

The ventral striatum and VMPFC showed no additional significant main effects or interactions (Appendix F).

Figure 5

Higher levels of manic symptoms are associated with greater outcome-locked activation in the a) right anterior insula modulated by mean of standard and mood-biased RPE and b) in the bilateral anterior insula modulated by mood-biased RPE



Note. MAS = Bech-Rafaelsen Mania Scale

3.4 Exploratory Whole-Brain Analyses

Within-group activations in healthy controls and participants with bipolar disorder for standard and mood-biased EV and RPE signals at a cluster-corrected threshold are presented below and summarised in Appendix G.

Because of the exploratory nature of our whole-brain analyses and the highly related constructs of standard and mood-biased EV and RPE, which would likely yield small effects, a less conservative p(uncorrected)< .001 threshold was used for between-group activations (Appendix H).

Standard and mood-biased EV- and RPE-modulated activations were not significantly correlated with either depressive or manic symptoms at the cluster-corrected level; results at the p(uncorrected)< .001 threshold are presented below and summarised in Appendix I.

3.4.1 Tracking of EV signals and group differences in tracking of EV signals during anticipation

Modulation of anticipatory activation by standard EV was observed only in controls and not in participants with bipolar disorder. Healthy controls exhibited significant clusters of activation in the right angular and inferior parietal gyri modulated by standard EV (Appendix G; Figure 6a-b). Neither group showed mood-biased EV-modulation of anticipatory activation even at p(uncorrected)< .001 (Table 3).

Healthy controls exhibited greater modulation of anticipatory activation by standard EV in the right paracentral lobule and by mood-biased EV in the left parahippocampal gyrus than participants with bipolar disorder (Appendix H; Figure 7a). Participants with bipolar

disorder exhibited greater modulation of anticipatory activation by mood-biased EV in the left calcarine (Appendix H; Figure 7b).

Standard EV-modulated activations in the right anterior insula and left caudate were negatively correlated with depressive symptoms and standard EV-modulated activity in the right caudate was positively correlated with manic symptoms (Appendix I). Mood-biased EV-modulated activity was not significantly correlated with either depressive or manic symptoms.

3.4.2 Tracking of RPE signals and group differences in tracking of RPE signals during outcome

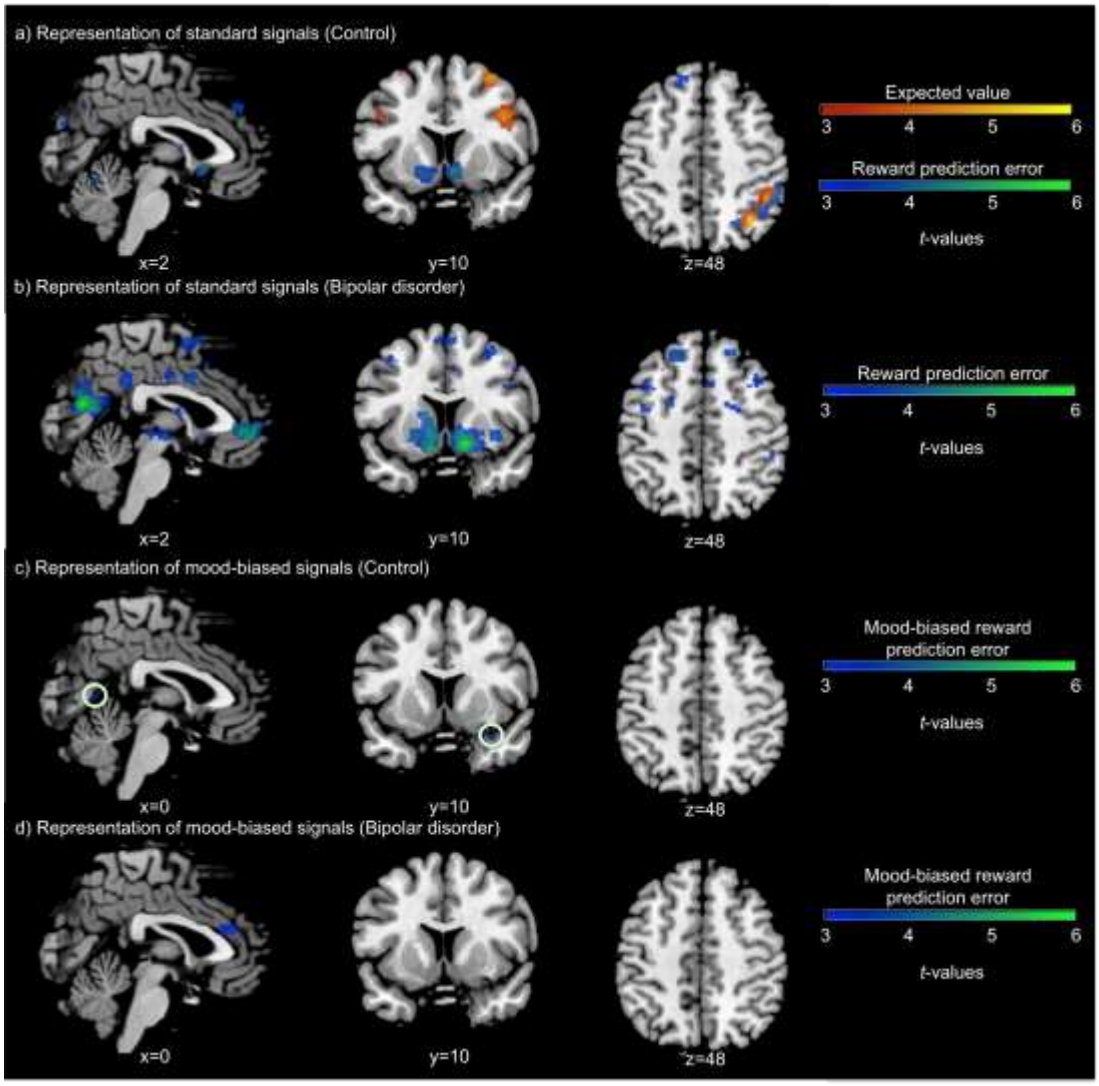
Modulation of outcome activation by standard RPE, but not mood-biased RPE, was observed in controls and participants with bipolar disorder. Healthy controls exhibited significant RPE-modulated activity in the right superior parietal and olfactory gyri whereas participants with bipolar disorder exhibited significant RPE-modulated activity across multiple regions including the precuneus, nucleus accumbens, anterior and middle cingulate cortices, middle temporal and frontal gyri (Appendix G; Figure 6a-b). Mood-biased RPE-modulation of outcome activation was observed in both groups only at an uncorrected threshold (Table 3; Figure 6c-d).

Participants with bipolar disorder exhibited greater modulation of outcome activation by standard RPE in the precuneus, middle temporal, supramarginal and lingual gyri, supplementary motor area, caudate, and anterior cingulate cortex and by mood-biased RPE in the right middle occipital gyrus than controls (Appendix H; Figure 7c). Only the standard RPE-modulated activity in the precuneus survived cluster-correction.

Standard RPE-modulated activations in the bilateral parahippocampal gyurs were positively correlated with depressive symptoms whereas standard RPE-modulated activity in the left thalamus and left precentral gyrus were negatively correlated with depressive symptoms (Appendix I). Standard RPE-modulated activity in the bilateral precuneus was negatively correlated with manic symptoms. Mood-biased RPE-modulated activity in the left nucleus accumbens was positively correlated with depressive symptoms whereas mood-biased RPE-modulated activity in the right inferior parietal gyrus and right precuneus were negatively associated with manic symptoms.

Figure 6

Modulation of within-group whole-brain activation by a) standard expected value and reward prediction error in healthy controls, b) standard reward prediction error in participants with bipolar disorder, c) mood-biased reward prediction error in healthy controls and d) mood-biased reward prediction error in participants with bipolar disorder



Note. Red-yellow and blue-green colours represent EV and RPE signals respectively. b) Only standard RPE-modulated activity in participants with bipolar disorder is shown, as standard EV-modulated activity did not survive cluster-correction; c-d) Across groups, mood-biased EV showed no significant activations at cluster-level or *p*(uncorrected)< .001 thresholds and mood-biased RPE-modulated activations did not survive cluster-correction.

Table 3

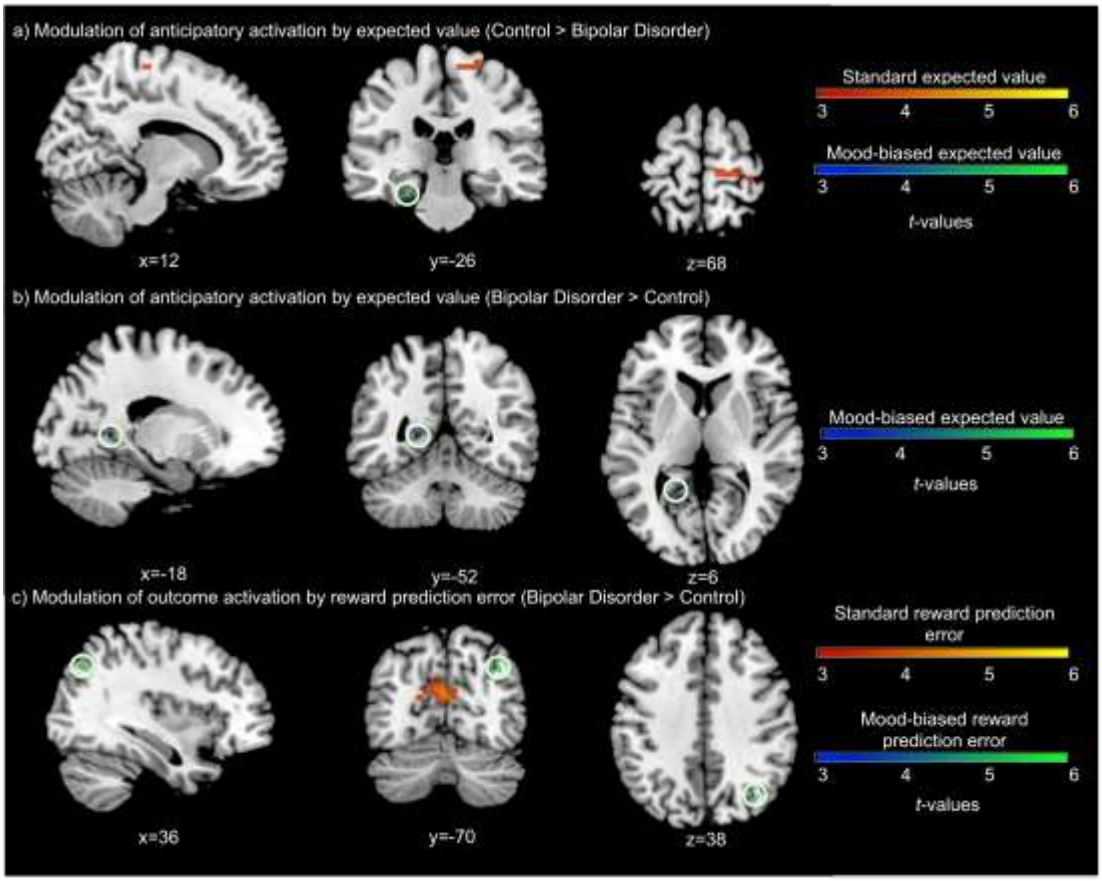
Within-group whole-brain activation of mood-biased EV and RPE at p(uncorrected)<. 001 threshold

			Peak MNI			
	Description of brain regions	k	x	y	z	*t*
Healthy controls						
Mood-biased EV	No significant within-group activations					
Mood-biased RPE	Left cuneus	18	-2	-78	22	3.89
	Left thalamus	17	-12	-24	4	3.73
	Right middle temporal gyrus	8	48	-40	2	3.72
	Left calcarine	6	-20	-76	8	3.69
	Left lingual gyrus	6	0	-64	4	3.47
Bipolar disorder						
Mood-biased EV	No significant within-group activations					
Mood-biased RPE	Right middle occipital gyrus	17	36	-70	38	4.11
	Left superior anterior cingulate cortex	60	0	30	20	3.77
	Right pregenual anterior cingulate cortex	28	10	44	18	3.76
	Right middle temporal gyrus	7	64	-26	-6	3.74
	Left precentral gyrus	5	-46	4	46	3.6
	Right putamen	6	22	0	8	3.47

Note. MNI = Montreal Neurological Institute; EV = expected value; RPE = reward prediction error

Figure 7

Group differences in the modulation of whole-brain anticipatory and outcome activation by standard and mood-biased signals, p(uncorrected)< .001



Note. Red-yellow and blue-green colours represent EV and RPE signals respectively.

4. Discussion

This study aimed to take account of momentary changes in mood and its effects in biasing the perception of reward in a clinical sample with bipolar disorder and matched controls. We utilised an existing neuro-computational model of mood (Eldar & Niv, 2015) to investigate whether mood-biased learning signals (EV and RPE) are represented in addition to non-mood-biased (standard) signals in the ventral striatum, anterior insula and VMPFC. We also examined whether mood-biased signals would be tracked more strongly in these regions in individuals with bipolar disorder than matched controls, and whether these effects are modulated by mood symptoms.

Overall, the results provide some evidence for greater representation of mood-biased signals in individuals with bipolar disorder. This is exemplified by group-level differences in the precuneus and occipital regions and positive modulation by mood symptoms as exemplified by increased activation in the anterior insula, ventral striatum, and parahippocampal gyrus, and the deactivation of regions that comprise the default-mode network (precuneus and posterior parietal cortex) (Broyd et al., 2009). As expected, both groups tracked standard RPE in all three ROIs, in line with previous findings (Chase et al., 2015; D'Astolfo & Rief, 2017; Garrison et al., 2013); notably, participants with bipolar disorder track standard RPE-modulated VMPFC activity more strongly than controls.

4.1 Mood-Biased Learning Signals and Modulation by Mood Symptoms

Whole-brain analyses under a less conservative threshold indicate that individuals with bipolar disorder track mood-biased RPE signals in several regions including the anterior cingulate cortex and putamen (i.e. dorsal striatum), which are implicated in selecting optimal actions based on learned associations to support goal-directed behaviour (Akam et al., 2021; Balleine et al., 2007). These results could therefore indicate the influence of

momentary mood on the recruitment of attentional and motor control processes, driven by momentary mood, involved in adjusting behaviour to achieve a desired goal. While ROI analyses found limited, representation of mood-biased signals in participants with bipolar disorder, healthy controls were shown to track mood-biased EV, and to a lesser extent, mood-biased RPE signals, in the ventral striatum and VMPFC respectively.

Whole-brain analyses additionally found some group-level differences, in which participants with bipolar disorder showed greater mood-biased EV- and RPE-modulated activity in visual processing areas (e.g. calcarine and middle occipital gyrus) than controls. This could indicate greater attentional engagement driven by momentary mood towards expected outcomes and RPEs. This view accords with previous studies documenting the impact of positive mood on the broadening of visual attention (Wadlinger & Isaacowitz, 2006), leading to greater mobilisation of effort in obtaining and seeking rewards in bipolar disorder (Johnson et al., 2017). Additionally, controls showed greater tracking of mood-biased EV signals than participants with bipolar disorder in the parahippocampal gyrus – a region involved in encoding and retrieving memory representations (Bohbot et al., 2015). This suggests greater integration of mood-biased RPE representations from previous trials in memory, resulting in more realistic expectations of future outcomes, rather than eliciting large mood fluctuations with each trial-wise RPE. It is important to note, however, that the above findings were under a less conservative threshold and begs further replication.

One possibility for the above pattern of results, in which mood-biased influences on learning signals were detected predominantly under a less conservative whole-brain threshold, could be higher heterogeneity within the bipolar disorder group. Indeed, we found evidence that differences in mood symptoms modulated several effects (see paragraphs below). In addition, mood-biased signals were computed assuming a moderate level of mood bias, which could still be adaptive (Eldar et al., 2016), and therefore not optimal for our task and clinical sample. Given that we approximated this level of mood bias from Eldar and

Niv (2015)'s healthy sample with higher mood instability, determined by a median split, it could be argued that half of our healthy participants would have the same levels of mood bias whereas participants with bipolar disorder would have stronger mood bias values. Therefore, using higher values of mood bias in future analyses might better discriminate the effects of mood-biased signals in individuals with bipolar disorder.

In our ROI analyses, we found that greater residual manic symptoms are associated with stronger mood-biased influences on RPE signals in the right anterior insula, which has previously been linked to reward-based salience (Wang et al., 2015). This is corroborated by our follow-up analyses, which found that model-estimated mood positively modulated outcome activation in the right anterior insula in participants with bipolar disorder, who trended towards showing greater activation than controls, consistent with previous findings (Rutledge et al., 2014). Whole-brain level analyses demonstrated that increased manic symptoms were associated with reduced mood-biased RPE-modulated PPC and precuneus activity, which is part of the default-mode network. This network is activated during the processing of internal mental states when individuals are not engaged in a task (Broyd et al., 2009). Our findings thus indicate that greater manic symptoms are associated with greater salience towards and task-focus during the perception of outcomes. Similarly, individuals with greater depressive symptoms track mood-biased RPE-modulated ventral striatum activity more strongly, suggesting greater mood-biased affective and motivational responses to outcomes (Rutledge et al., 2014). Individuals with more depressive symptoms also show increased and decreased tracking of standard RPE signals in regions involved in memory (parahippocampal gyrus) and motor processing (thalamus and primary motor cortex) respectively (Wang et al., 2020). This may suggest greater encoding of RPEs in memory, which fails to translate to optimal planning and execution of goal-directed behaviours.

Notably, while higher levels of depressive symptoms were associated with decreased standard EV-modulated activation in the caudate and anterior insula, higher levels of manic

symptoms was associated with increased caudate activity. The caudate, part of the dorsal striatum, is implicated in selecting actions contingent upon learned action-outcome associations (Balleine et al., 2007). This dissociation could suggest that manic symptoms promote greater salience towards outcomes and mobilisation of effort towards selecting actions that promote reward-seeking and vice-versa for depressive symptoms. However, further work, in which separate positive and negative EV signals are regressed against dorsal striatum activation, is warranted to confirm this, as in our study, EV was modelled as the net value of positive and negative EVs (for potential rewards and losses respectively).

Taken together, we found that residual manic symptoms and momentary mood biases the perception of outcomes, highlighting the impact of mood states on mood bias i.e. an individual with greater mood symptoms will experience a stronger effect of mood bias on reward perception. One could argue that these manic symptoms represent trait-level mood rather than mood states. As such, our findings in which anterior insula activity is modulated by manic symptoms could reflect a trait-based mechanism such that individuals with greater manic symptoms have a stronger trait-level mood bias. In line with this, Mason and colleagues (2017) proposed that strong mood biases represent vulnerability factors that generate and maintain mood symptoms in bipolar disorder. However, further longitudinal studies are warranted to assess whether the tendency for mood to bias reward perception varies with fluctuating mood states or manifests as a trait.

4.2 Differences in the Representation and Propagation of Standard Learning Signals

Both ROI and whole-brain analyses indicate that compared to controls, individuals with bipolar disorder showed stronger RPE-modulated activity in the VMPFC and precuneus respectively, with the latter finding surviving cluster-correction. This could suggest greater emotional impact of discrepancies between expectations and outcomes (Rutledge et al., 2014). Other reward task-fMRI studies have interpreted outcome-locked precuneus

activation as indexing arousal levels and reward responsivity (Bradley et al., 2017; Koch et al., 2018). Individuals with bipolar disorder could thus be oversensitive to RPEs, updating expectations abruptly, which could trigger marked mood fluctuations and goal-directed behaviour. For instance, successive wins on a roulette game may result in the overgeneralisation of these better-than-expected outcomes and inflated expectations of experiencing future events of low probability (e.g. winning the lottery). Previous studies show that individuals with bipolar disorder perform comparably to controls on behavioural measures of reinforcement-learning (Barch et al., 2017; Lewandowski et al., 2016; Strauss et al., 2015); however, one study reported that individuals who most recently experienced a manic rather than depressive episode showed increased sensitivity to outcomes and vice-versa (Linke et al., 2011). Notably, there might be other mechanisms (top-down attentional or cognitive processes) beyond the biasing effect of momentary mood on reward perception that might explain the increased RPE-modulated activity in participants with bipolar disorder.

Although ROI and whole-brain analyses suggest that individuals with bipolar disorder robustly track standard RPEs, and to a lesser extent, mood-biased RPEs, they show modest representation of EV signals. This could suggest that, unlike healthy controls, individual with bipolar disorder show a lack of integration of trial-wise RPEs and updating of value representations. As a result, it could be that such failures in integration maintain unrealistic expectations of outcomes, which generate further mood instability when those expectations are not met (Mason et al., 2017). Our findings potentially suggest more efficient cross-talk between regions tracking standard RPE (ventral striatum, anterior insula, VMPFC) and EV (VMPFC), which is likely the final common pathway for selecting goal-directed actions and choices (Gläscher et al., 2009). This is corroborated by whole-brain analyses, in which only controls showed overlapping standard EV and RPE-modulated activity in the posterior parietal cortex (PPC) – a region posited to orient attention towards reward-associated visual representations of choices during decision-making (Sacré et al., 2017).

However, in order to derive directional relationships of how learning signals are propagated between regions, studies using analysis techniques that model causal relationships between brain regions (e.g. dynamic causal modelling) are warranted. Moreover, there remains an open question pertaining to how mood-biased learning signals are propagated across brain regions and whether it is distinct to how standard signals are propagated. It would be interesting to investigate if the propagation of mood-biased learning signals among the ventral striatum, anterior insula and VMPFC show alterations between individuals with bipolar disorder and healthy controls. Understanding these functional neural dynamics would facilitate the identification of precise network-level mechanisms underlying mood instability in bipolar disorder, which can be targeted with better efficacy in clinical intervention. Moreover, further research can examine how these network dynamics change across contexts (e.g. across development, within and out-of-episode, and after treatment).

Alternatively, another possibility that could explain the relatively weak representation of EV signals in general is the greater tracking of negative EV signals across participants. In support of this, previous research demonstrated that losses are weighted more heavily than gains of similar value (i.e. loss aversion) (Kahneman & Tversky, 1979). Additionally, other computational work suggests that negative RPEs exert greater influences than positive RPEs in modulating (decreasing vs. increasing) gambling behaviour (Otto et al., 2016). Future work could therefore apply a model, which regresses positive and negative EV and RPE values separately. More robust representation of mood-biased signals could also be obtained if mood is modelled and initialised as a value based on participants' mood symptoms such that negative mood values are modelled for individuals with higher levels of depressive symptoms and vice-versa for manic symptoms.

4.3 Strengths and Limitations

This is the first study to apply a neuro-computational model of mood to fMRI data in a clinical sample and to examine effects of momentary mood in the loss domain. However, our findings should be interpreted within the context of several limitations. First, we utilised a paradigm with explicit cues that reduces behavioural differences attributed to learning effects, which meant that we could not estimate each participant's learning rate parameter, and derived mood bias and learning rate parameters from Eldar and Niv (2015)'s sample. As such, this precluded being able to confirm that the mood bias and learning rate parameters we selected explained participants' momentary mood and choices, which could have underestimated inter-individual variability. Alternatively, a future study could use a different task, in which learning rate and mood bias parameters for each participant could be derived; this was not feasible in this study, which is a secondary analysis of an existing dataset. However, a recent study suggests that regressing individual learning rates yields minimal changes to results (Wilson & Niv, 2015). Moreover, the mood-biased reinforcement-learning model has been validated in Eldar and Niv's (2015) study, and we additionally confirmed in our further analyses that model-estimated mood is tracked by the anterior insula, in line with previous studies (Rutledge et al., 2014; Vinckier et al., 2018).

Second, given that this is the first study to implement Eldar and Niv (2015)'s neuro-computational model within a clinical population, the findings of this study should be considered as preliminary and holds no immediate clinical utility. Third, although our power analysis suggests that an implied power of 89% was achieved with our sample size (N=42), our findings could be restricted to this dataset and may not be generalisable across other populations. Further replication with larger sample sizes in future task-based fMRI studies of clinical populations are therefore warranted. Fourth, this study did not control for the potentially confounding effects of medication on reward-related neural activity. Although this was partially mitigated through the exclusion of individuals who used antipsychotic medication, future studies could examine reward processing in unmedicated or medication-naïve individuals with bipolar disorder.

4.4. Conclusion

In summary, our findings provide some evidence that individuals with bipolar disorder track mood-biased RPEs more strongly than controls, and this tendency was increased in those with greater manic symptoms. We also found that individuals with bipolar disorder who were out-of-episode track violations of expectations in relation to outcomes (i.e. RPEs) more closely than healthy controls. However, unlike healthy controls, they show limited integration of these RPEs and updating of standard and mood-biased value representations.

4.4.1 Implications for future research and clinical practice

Given the null findings reported in relation to the ROI analyses, the results of this study could inform hypotheses for future research to more thoroughly investigate whether these brain regions represent mood-biased EV and RPE signals in individuals with bipolar disorder. As our study was conducted with individuals who were out-of-episode, further studies are needed to assess the role of dynamic mood states in biasing reward perception in bipolar disorder within (hypo)manic and depressive episodes and how that might relate to dysregulated goal-directed behaviour. Additionally, longitudinal studies are needed to examine the degree to which reinforcement-learning in bipolar disorder is modulated by trait-level differences in mood instability versus momentary changes in mood. At present, the findings of this study hold no direct implications for clinical practice. However, with further replications and studies, future clinical fMRI studies could yield findings that hold more immediate implications for interventions for bipolar disorder. For instance, a recent study has shown that interventions that target reward-driven attentional processes, such as mindfulness, have been shown to down-regulate RPE signals in the brain (Kirk et al., 2019)..

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Part 3: Critical Appraisal

1. Introduction

This critical appraisal discusses key themes that arose during the research process. First, researcher influences and positionality will be highlighted. Second, the relevance of understanding mechanisms underlying psychological distress and those that promote recovery will be discussed in relation to the present research. Third, the promises and pitfalls of neuroimaging and computational psychiatry research and its current application to psychological clinical practice will be presented. Finally, general recommendations for clinical fMRI research are summarised.

1.1 Influences on the Present Research

Before starting clinical training, I was a research assistant in a clinical neuroimaging lab, which conducted studies using functional magnetic resonance imaging (fMRI) and investigated the neurobiological mechanisms underlying substance use disorders. I was there for a yearlong placement as part of my master's programme and during my time there, I thoroughly enjoyed the research process and even participated in several neuroimaging studies as a participant. As a novice who did not have prior programming experience, I found neuroimaging analyses to be challenging at times and was often learning through trial and error. However, I found it exciting to be using innovative and novel techniques in the pursuit of understanding the relationship between brain and behaviour, especially when it has the potential to contribute to the refinement and development of clinical interventions.

Whilst I was on my research placement, I was introduced to multiple perspectives of psychological theory and the possibility for integrating disciplines that I had thought could not be reconciled e.g. neuropsychoanalysis. This value of integration is what propels me to further my interests and skills in conducting clinical neuroimaging research. As a person who had graduated university and was undecided about pursuing either a research or clinical

career, my experiences have led me to pursue and hold more of a both/and position. As a trainee clinical psychologist, I recognise the importance of conducting service-level research and generating practice-based evidence to improve and inform clinical practice. In tandem, I also aspire to use my unique position as a clinician to engage in clinical neuroscience research, which at times have been criticised as being too reductionist (Krakauer et al., 2017). This research project was thus congruent with my prior experiences with neuroimaging research and my personal and professional values of integrative working and thinking.

1.2 The Importance of Understanding Mechanisms

Throughout my involvement in this research, I thought about the link between my therapeutic work with services users and the psychobiological mechanisms underlying the development and maintenance of psychological distress, and importantly, those that promote the alleviation of psychological distress. In my personal clinical experience, I find that service users I have worked with appreciated formulations, which included both psychological and neurobiological levels of explanation, though notably, this may not always be the case for all service users. In my work with children and families, I use Dr Dan Siegel's Hand Model of the Brain (Siegel & Hartzell, 2013), to explain how the brain perceives and copes with threat and trauma, which affects how we regulate emotions. Including such explanations to explain how our cognitions, physiological sensations and emotions are interlinked may be helpful for some service users in understanding how and why we may feel certain emotions within certain contexts. Conducting research that further elucidates brain-behaviour relationships may provide a deeper understanding of such mechanisms, which can be included in clinical formulations to help normalise and validate service users' experiences.

A number of recommendations have been suggested for the future of mental health research including the importance of elucidating shared and dissociable mechanisms underlying the development and maintenance of psychological distress and existing psychological interventions across multiple disciplines and levels of analysis, including genes, neural structure and function, behaviour, self-report and interviews (Holmes et al., 2018; Insel et al., 2010). Returning to research focusing on mechanisms could potentially contribute to the improvement of clinical interventions. For instance, computational modelling frameworks such as the application of reinforcement learning models could be used to understand mechanisms that generate and maintain psychological distress (Nair et al., 2020), and examine whether these mechanisms are shared across disorders (Zald & Treadway, 2017). Reinforcement learning models could potentially be used to evaluate existing psychological therapies such as CBT (Nair et al., 2020) and mindfulness (Kirk et al., 2019), and explain why certain people may not benefit from certain therapies (Moutoussis et al., 2018). As such, understanding how symptoms of psychological distress manifest within and across disorders and why psychological therapies work for some and not others could help towards refining interventions that better target agents of change, have broad utility across disorders, and afford greater precision in tailoring interventions to individuals (Dalgeish et al., 2020).

In relation to shifting the focus on mechanistic research, the meta-analysis and empirical study both examine psychobiological processes underlying psychological distress, at the level of functional brain activity. While the former adopted a transdiagnostic approach and examined shared processes underlying dyregulated goal-pursuit and reward processing across disorders, the latter focused on using computational modelling approaches to fMRI data to examine mechanisms underlying mood instability in bipolar disorder.

Findings from the empirical study provide encouraging evidence that momentary mood fluctuations affect how individuals perceive reward (e.g. higher or lower than its actual

value). This is evident by reward-related brain activity in several regions including the anterior insula, which was found to be modulated by mood (manic and depressive) symptoms and model-estimated mood. This mood bias effect is posited to be an adaptive mechanism, which allows for optimal decision-making and goal-pursuit (Eldar et al., 2016). Based on Mason and colleagues (2017)'s neuro-computational framework, the presence of an inherently strong mood bias is proposed to result in unrealistic expectations of future outcomes, resulting in manic episodes when momentary mood is elevated and depressive episodes when momentary mood is low in bipolar disorder. Our findings lend support to this model: individuals with bipolar exhibit greater mood-biased influences on the perception of outcomes than controls, exemplified by stronger activity in visual processing areas. However, this specific finding is reported at a less conservative threshold, uncorrected for multiple comparisons, which inflates the chances of finding false positives – a common issue in neuroimaging research that will be discussed in the next section. Therefore, further sufficiently powered studies with larger samples are warranted to further characterise mood bias influences on reward perception in individuals with bipolar disorder.

On reflection, it is important to note that the empirical study applied a neuro-computational model of mood to fMRI data within a controlled experimental setting. A computational model, which claims to explain mood instability within the context of task performance, should generalise its findings to predict real-world fluctuations in momentary mood (Nair et al., 2020). As such, researchers have argued for the use of ecologically valid tasks in elucidating the psychobiological mechanisms underlying symptoms of psychological distress and developing mechanism-focused interventions (Scholl & Klein-Flügge, 2018). There remains an open question as to whether the neuro-computational model applied in our study is predictive of real-world momentary mood fluctuations that unfold over a naturalistic timescale, which could be the focus of future research.

Notably, both the empirical study and the meta-analysis investigate mechanisms at the level of functional brain activity. While the former focused on psychobiological mechanisms underlying mood instability in one disorder (i.e. bipolar disorder), the latter focused on shared processes underlying dysregulated reward processing across psychiatric disorders. Reflecting on this level of analysis (i.e. task-dependent functional brain activity), both studies have identified putative brain regions that underpin specific psychobiological mechanisms underlying dysregulated reward processing and mood instability; however, they do not reveal information about how these regions may interact with each other. Importantly, these psychobiological processes likely involve multiple brain regions and networks. Approaches that aim to find evidence for directional relationships and functional connectivity between brain regions (e.g. Dynamic Causal Modelling) can extend findings of local activation to network-level connectivity. Such functional coupling between regions could be measured across different contexts – for instance across developmental stages and following therapy. Integrating research from multiple levels of analysis therefore could bring about greater understanding of the mechanisms underlying psychological distress.

In addition to understanding the mechanisms that contribute to the maintenance of psychological distress, it is important to understand how existing clinical interventions work. Although there is a large body of evidence that psychological treatments are effective for individuals experiencing mental health difficulties, there is significant variation in treatment response. Understanding why and how psychological interventions work is therefore integral because it could help clarify which service users would benefit from specific types of intervention i.e. what works for whom and under what circumstances (Holmes et al., 2014). An increasing body of neuroimaging research is focusing on identifying treatment-related mechanisms, and has highlighted the role of top-down frontal cortical regions in modulating activity in limbic regions, which are altered following therapy across modalities (Marwood et al., 2018; Mason et al., 2016; Perez et al., 2016). However, while fMRI has provided emerging insights into the potential mechanisms underlying intervention and the

maintenance of psychological distress, it is important to be aware the potential challenges involved in conducting neuroimaging research, which are discussed below.

1.3 Potential Challenges and Pitfalls of Functional Neuroimaging

Functional neuroimaging, particularly, fMRI, has been considered a ground-breaking non-invasive tool for gaining insight into the inner workings of the brain since its inception nearly three decades ago (Rosen & Savoy, 2012). Measuring brain activity associated with specific cognitive processes while the brain is engaged in a task (i.e., task-fMRI) has provided researchers greater insight into the neural bases of human behaviour and the opportunity to study individual differences in brain function and how that might relate to differences in behaviour (Matthews et al., 2006). The logic is as follows: If a brain region, such as the ventral striatum, is activated during a reward task, the differences in the extent to which this region is activated between individuals, is posited to reflect differences in reward sensitivity and goal-directed behaviour (Schreuders et al., 2018). Hence, fMRI became heralded as a tool for studying how the brains of individuals differ (e.g. across development), and therefore is posited to hold great promise for identifying neural processes underlying psychiatric disorders (Canario et al., 2021; Habecker et al., 2016; Saeed, 2018).

During the process of reviewing the current fMRI literature investigating reward-related brain activation and interpreting the findings of the present research, several key themes were observed, particularly in relation to the replicability of task-fMRI findings, interpretation of fMRI results, and the gap between research and clinical translation.

1.3.1 The fMRI replication crisis and false-positive neuroimaging

In parallel with psychological research in general (Nosek et al., 2021), fMRI research has been experiencing a crisis of replication (Hong et al., 2019). Replication refers to testing

the reliability of an existing finding across independent samples, thereby protecting against false positives and negatives and contributing to greater validity of scientific findings (Pernet & Poline, 2015). Unfortunately, researchers have little incentive to conduct replication studies due to certain systemic factors, namely, the privileging of novel and statistically significant findings by scientific journals over replicable and non-significant ones (Evans, 2017). Moreover, the inherent high cost and time-intensive process of data collection in fMRI research may deter researchers from attempting to replicate studies (Turner et al., 2018).

Indeed, a recent study reported that more than half of neuroimaging findings in the cognitive neuroscience and psychology disciplines likely represent false positives (Szucs & Ioannidis, 2017). FMRI studies often have low sample sizes (e.g. n<20), which contribute to inadequate statistical power and overestimated effect sizes and make findings less likely to be successfully replicated (Szucs & Ioannidis, 2020). This was evident across the studies included in the meta-analytic review, 40% of which had sample sizes of less than 20 in each group and most of which did not report a formal power analysis. Similarly, the empirical study had a sample size of 21 participants in each group.

One of the main culprits of false-positive neuroimaging is a construct known as "researcher degrees of freedom" (Simmons et al., 2011) – the undisclosed flexibility in the ways that fMRI analysis is conducted. Often, the analysis of fMRI data entails various choices that seem arbitrary – the type of analysis software used, pre-processing and analysis pipelines and correction for multiple comparisons, among others (Wicherts et al., 2016). For instance, Carp (2012) demonstrated that slightly altering the parameters during analysis yielded 6,912 different analysis protocols. Therefore, the opportunistic use of such methodological flexibility in the pursuit of obtaining statistically significant findings have large impacts on study outcomes, thus inflating false-positive findings and limiting replicability of fMRI findings (Hong et al., 2019). Additionally, errors in analysis and coding are easy to make, especially for researchers such as myself who have limited programming background.

Several initiatives have been proposed to encourage open sharing of neuroimaging data and code to increase transparency and replicability of results (e.g. Neurovault, Open fMRI, GitHub, etc.) (Pernet & Poline, 2015).

In the meta-analytic review, I endeavoured to reduce the flexibility of analysis by closely adhering to Müller and colleagues' (2018) recommended guidelines for conducting fMRI meta-analyses, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Additionally, in the empirical study, detailed information was provided with regards to fMRI data acquisition, first-level and second-level analyses and the computational model formula applied to the data, as recommended by Poldrack and colleagues' (2008) guidelines for reporting an fMRI study. Adhering to these guidelines aimed to facilitate the transparency of the methodological choices made and future replicability. In order to minimise errors wherever I could, I used the batch mode wherever possible on Statistical Parametric Mapping (SPM) so that I could save scripts and code and use them to re-run the same analysis, thereby facilitating reproducibility of results. However, on reflection, the lack of pre-registration and pre-specification of hypotheses and planned analyses precluded maximal transparency of the research conducted and thereby may reduce the trust that other researchers place in the reported findings of this research. Additionally, it perpetuates the systemic issues around researcher degrees of freedom and other problematic research practices (Pernet & Poline, 2015).

1.3.2 Interpreting fMRI results

It is argued that one of the potential pitfalls in fMRI research is the way inferences are drawn. The typical interpretation made in fMRI studies is that when a cognitive process happens, specific brain regions engaged in that process become active and that pattern of brain activity is what is captured by fMRI. The reverse of this, in which an interpretation is made regarding the involvement of a cognitive process, which is not directly tested, simply

based on observed brain activity (i.e. reverse inference) can be quite misleading (Poldrack, 2006). Similarly, null findings can lead researchers to fallaciously conclude an absence of effects. Many neuroimaging studies, including the present research, use similar reverse inferences to account for the occurrence of unexpected regions of activation. For instance, in the meta-analysis, the decreased temporal pole activation observed across psychiatric disorders compared to control groups during loss anticipation was a relatively unexpected finding, which prompted some speculation about what this activation meant using other studies that have found similar activation in this area.

Reverse inferences make a strong assumption that there is a one-to-one mapping between brain structure and function and its success is contingent upon the degree of functional specialisation of the brain region in question (Henson, 2005). In other words, the more a region is involved in multiple cognitive processes, the less certain one can be about the engagement of a particular cognitive process when activation within this region is observed (Schleim & Roiser, 2009). Therefore, interpretations that comprise reverse inferences are weaker and such inferences should be interpreted with caution and treated as a working hypothesis that requires further evaluation. Making reverse inference interpretations is a common pitfall in fMRI research and, speaking from my limited experience in this field, one way to develop sound interpretations is through collaboration, especially with individuals from different disciplines.

1.3.3 FMRI in translation: the wide gap between research and clinical application

Often, the stated objective of a large proportion of fMRI and neuroscience research within psychology is to achieve translation of findings into clinical practice in order to improve diagnosis and clinical intervention. Since its inception, there has been a notable paradigm shift in psychiatric research towards a dimensional and transdiagnostic approach to psychiatric diagnosis and away from traditional symptom-based classifications (Insel et al.,

2010). However, although a substantial body of fMRI research includes psychiatric populations, often with compelling findings, the impact of fMRI in psychological clinical practice is still minimal. At present, fMRI research is still at the stage of identifying and validating neurobiological mechanisms underlying psychiatric disorders.

As highlighted above, the poor replicability of fMRI findings and high cost of fMRI scanning are some of the factors that limit its application to clinical practice. In addition, perhaps the gap in clinical translation partly lies with the novelty and availability of compelling tools in neuroscience, which may obscure the very objective it sets out to achieve. Some researchers suggest that advances in neuroscience has seen a rise in technique-driven research (Krakauer et al., 2017) and within the context of mental health research may run the risk of being too reductionist (Borsboom et al., 2018). Psychological distress can be explained not just via neurobiological processes but also via various contextual factors (sociocultural influences, past experiences, inter-generational family narratives, systems of privilege and oppression, etc.) in which individuals are situated within and construct meaning (Marková, 2018). Given the massively multi-faceted aspects and transdiagnostic mechanisms that underpin psychiatric disorders, a comprehensive understanding of the multiple mechanisms underlying psychiatric disorders will require the integration of pluralist accounts (Kendler, 2008). This highlights the need for cross-discipline collaboration in order to inch closer towards bridging the gap between research and clinical translation. For instance, finding collaborators with the technical knowledge of neuroimaging research and statistical and computational modelling, could result in better study design and preprocessing methodology to improve the validity and reproducibility of findings. Similarly, fostering collaboration with clinicians may help in integrating computational frameworks with psychological theory and refining research hypotheses.

On reflection, the ways in which fMRI research questions are posed and how conclusions are drawn depend on the epistemological stance of the researcher, one's

training background and familiarity with fMRI research. Given my limited experience in neuroimaging research and programming, the research process was largely focused on navigating the complex terrain of fMRI research and analysis: developing an understanding of computational modelling in the study of mood and reward, learning how to use multiple software packages for fMRI meta-analysis and the empirical study and troubleshooting errors and re-running analyses. As such, it was easy to lose sight of the ambitious ideals of using my position as a clinician to use a psychological framework to inform the undertaking of this present research, as I was focused on the technical aspects of the project. This included taking little time in reconciling and reflecting on the tensions related to my epistemological position as a researcher conducting neuroimaging research and as a clinician who (hopefully) draws from a social constructivist approach.

1.4 Conclusions and Recommendations For Future Research

Neuroimaging research provides a method to identify psychobiological mechanisms underpinning psychiatric disorders and clinical interventions, which holds implications for the improvement of existing interventions and the development of novel treatment approaches. The integration of psychological and neurobiological accounts of mental health difficulties allows for the development of richer formulations that can be used in clinical practice. Although neuroimaging research holds significant promise, at present, much of neuroimaging research is still focused on expanding current understanding of neural mechanisms underlying psychological processes and clinical phenomena. For neuroimaging research to be reach clinical translation, efforts should be directed by researchers as well as journal and funding agencies to support the replication of findings and encourage sound research practices, which include pre-registering the study and planned hypotheses, and open sharing of data or code. Furthermore, for neuroimaging research to achieve clinical utility, it is imperative to foster collaboration between individuals from different disciplines (e.g. clinicians, neuroscientists, statisticians, engineers, etc.) and those using a range of

research methods (e.g. quantitative, qualitative and mixed-methods). This is a monumental task and it is no surprise why it is challenging to bridge the wide gap between neuroimaging research and clinical practice; however, I believe such integration of thinking and working is essential before clinical translation can be achieved.

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Appendices

Appendix A: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	11-12
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	12-13
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	12,23,24
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	23-24
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	25-26
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	25
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	25
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	25-26
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	24,26
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	26
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	27
Summary measures	13	State the principal summary measures (e.g., risk ratio,	11,25,27

		difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	27-29

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	28-29
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	28-29
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	30-31
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	32-34
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	38,41,43
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	36-43
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	42
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	42-45
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	46-56
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	53-55
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	55-56
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix B: FMRI data acquisition and analysis parameters of included studies

Authors	Scanner	Tesla	Slices	Slice thickness	TR ms	TE ms	Software	FWHM	Stereotaxic space	Statistical threshold
Abler et al. 2008	Siemens Trio	3	21	3	1500	35	SPM2	8	MNI	Uncorrected, $p<.005$
Arrondo et al. 2015	Siemens Trio Tim	3	32	-	2000	30	FSL	6	MNI	Corrected, $p<.05$
Balodis et al. 2013	Siemens Trio Tim (2 scanners)	3	25	4	1500	27	SPM5	6	MNI	Corrected, $p<.05$
Becker et al. 2017	Siemens Magnetom Trio	3	28	4	2000	30	SPM8	6	MNI	Uncorrected, $p<.001$, k=20
Carl et al. 2016	General Electric	3	34	-	1500	30	FSL	5	MNI	Corrected, $p<.005$, $z>4.0$, $k\geq10$
Choi et al. 2012	Siemens AVANTO	1.5	21	-	2340	52	SPM8	4	MNI	Corrected, $p<.05$
da Silva Alves et al. 2013	Philips system	3	35	3	2000	30	SPM8	8	TAL	Corrected, $p<.05$
DelDonno et al. 2019	General Electric Signa	3	29	4	2000	30	SPM8	5	MNI	Corrected, $p<.05$
Dichter et al. 2012	General Electric	3	32	-	2000	30	FSL	5	MNI	Corrected, $p<.005$, $k=10$, $z>2.58$
Herbort et al. 2016	Siemens Trio Tim	3	37	3	2000	30	SPM8	8	MNI	Corrected, $p<.05$
Johnson et al. 2019	General Electric Signa	1.5	24	4	2000	40	AFNI	4	TAL	Corrected, $p<.05$
Jung et al. 2011	Siemens AVANTO	1.5	25	5	2340	52	SPM2	4	MNI	Corrected, $p<.05$
Kaufmann et al. 2013	Siemens Sonata	1.5	33	-	1870	40	SPM8	8	TAL	Corrected, $p<.01$
Kirschner et al. 2020	Philips Achieva	3	38	3	2000	25	SPM8	6	MNI	Corrected, $p<.05$

Knutson et al. 2008	General Electric	1.5	24	4	-	40	AFNI	4	TAL	Corrected, *p*<.05
Li et al. 2018	Siemens	3	31	-	2000	30	SPM8	8	MNI	Corrected, *p*<.001
Nawijn et al. 2016	Philips Achieva	3	37	3	3000	27.63	SPM8	8	MNI	Corrected, *p*<.05
Pizzagalli et al. 2009	Siemens Symphony/Sonata	1.5	35	3	2500	35	FS-FAST	6	MNI	Corrected, *p*<.05
Schiller et al. 2013	General Electric	3	32	4	2000	30	FSL	5	MNI	Corrected, *p*<.05
Schreiter et al. 2016	Siemens Trio	3	28	4	2000	30	SPM8	9	MNI	Corrected, *p*<.05
Simon et al. 2016	Siemens Trio Tim	3	30	3	2000	30	SPM8	8	MNI	Corrected, *p*<.05
Smoski et al. 2011	General Electric 4T LX Nvi	4	34	-	1500	31	FSL	5	MNI	Corrected, *p*<.05
Stepien et al. 2018	Philips Achieva	3	38	3	2000	25	SPM8	6	MNI	Corrected, *p*<.05
Subramaniam et al. 2015	Siemens Trio Tim	3	35	-	2400	30	SPM8	8	MNI	Corrected, *p*<.05
Urosevic et al. 2016	Siemens Trio Tim (2 scanners)	3	34	-	2000	28	FSL	8.77-9.19	MNI	Corrected, *p*<.05
Yip et al. 2015	Siemens Trio	3	25	4	1500	27	SPM8	6	MNI	Corrected, *p*<.05

Note. TR = repetition time; TE = echo time; FWHM = full-width at half-maximum; MNI = Montreal Neurological Institute; TAL = Talairach and Tournoux Atlas; SPM = Statistical Parametric Mapping; FSL = FMRIB Software Library; AFNI = Analysis of Functional NeuroImages; FS-FAST = FreeSurfer Functional Analysis Stream

Appendix C: Monetary incentive delay task parameters of included studies

Authors	Magnitude	Number of trials	Cue duration (ms)	Anticipation duration (ms)	Target duration (ms)	Fixation cross duration (ms)	Outcome duration (ms)	Intertrial Interval (ms)	Hit rate %
Abler et al. 2008	$ .40, 1.25	120	750	3000	1500	-	1500	-	60
Arrondo et al. 2015	£ .01, 1	60	-	-	-	-	-	2000-6000	
Balodis et al. 2013	$ 0, 1, 5	110	1000	3000-5000	-	4000-6000	1200	-	66
Becker et al. 2017	€ 2	40		6000	-	-	-	6000-9000	
Carl et al. 2016	$ 2	40	2000	2000-2500	0-500	-	3000	-	66
Choi et al. 2012	₩ 0, 1000	-	350	4180-4480	200-500	-	1500	5170-9850	
da Silva Alves et al. 2013	€ .20, 1, 5	144	-	-	160-350	-	-	-	-
DelDonno et al. 2019	$ .20, 5	100	500	2000	250 (tailored to individual response time)	1750-3750	2000	4000	50-80
Dichter et al. 2012	$ 1	160	2000	2000-2500	0-500	-	3000	-	66
Herbort et al. 2016	€ .50, 10	204	1000	500-3500	520-600	500-3500	750	1000-4000	66
Johnson et al. 2019	$ .20, 1, 5	180	2000	2000-2500	150-470	1030-2350	2000	-	66
Jung et al. 2011	₩ 0, 1000	-	350	4180-4480	200-500	-	1500	5170-9850	-
Kaufmann et al. 2013	€ .10, .60, 3	144	250	3740-4240	150-500	1420-1720	1870	3280-3780	66
Kirschner et al. 2020	CHF .40, 2	72	750	2500-3000	-	-	2000	1000-9000	-

Knutson et al. 2008	$ 0, .20, 1, 5	180	250	2000-2500	160-360	-	1650	-	66
Li et al. 2018	-	60	250	2000-2500	-	300-3500	-	-	60
Nawijn et al. 2016	€ 1 (win) € .50 (loss)	162	1000-3000 (cue merged with anticipation)		Tailored to individual response time	1000	1500	1000-3000	66
Pizzagalli et al. 2009	$ 1.96 - 2.34 (win) $1.81- 2.19 (loss)	120	1500	3000-7500	Tailored to individual response time	4400-8900	1500	3000-12000	50
Schiller et al. 2013	$1	160	2000	2000-2500	500	-	3000	-	66
Schreiter et al. 2016	€ 2	-	6000 (cue merged with anticipation)		100	-	3000	-	-
Simon et al. 2016	€ .20, 1	220	750	3000	1000	-	1500	1000-8000	-
Smoski et al. 2011	$ 1	80	2000	2000-2500	500	-	3000	-	66
Stepien et al. 2018	CHF .40, 2	72	750	2500-3000	1000	-	2000	1000-9000	-
Subramaniam et al. 2015	$ 1	180	500	2000-8000	500	500	1500	2000-8000	68
Urosevic et al. 2016	$ .25, 1, 5	60	250	2000-2500	180-280	~1500	1650	100	70
Yip et al. 2015	S 1, 5	110	1000	3000-5000	Tailored to individual response time	3000-5000	1200	-	67

Appendix D: Computational model formula

Standard reinforcement-learning model

In the standard model, reward expectations were formalised as the net expected value (EV) of the possible outcomes; that is the probability and value of winning the sum of money at stake combined with the probability and value of losing this stake (see Table 1). Reward prediction error (RPE), was operationalised as the difference between the actual outcome value (R) obtained and the expected value i.e. RPE = R – EV.

Mood-biased model

To account for effects of mood on valuation, the standard model is modified to compute mood-biased RPEs using perceived (mood-biased) outcome value (Rmood-biased) instead of the objective outcome (R) (Eldar & Niv, 2015). In addition, we allowed mood on each trial to influence EV, leading to estimates of mood-biased net expected value (EVmood-biased) for each trial.

$$R_{mood\text{-}biased} = R * mbias^{mood(t)} \quad (1)$$

$$RPE_{mood\text{-}biased} = R_{mood\text{-}biased} - EV_{mood\text{-}biased} \quad (2)$$

Here, mbias is the mood bias parameter that indicates the direction and degree of mood bias. If mbias = 1, mood does not bias the perception of reward or expected value. With mbias > 1, mood exerts positive feedback i.e. reward is perceived as larger in a good mood and smaller in a bad mood, whereas the reverse is true with 0<mbias<1 would correspond to a negative feedback on reward value. In our present study, we set mbias to 1.2, based on the average mbias derived from Eldar and Niv (2015)'s sample of healthy participants who scored relatively high on the Hypomanic Personality Scale (determined by a median split) (Eckblad & Chapman, 1986), a measure of trait mood instability.

Before applying mood to R and EV, we constrained mood using a sigmoid function, allowing it to take values between -1 and 1: mood = tanh(mood)

$$EV_{mood\text{-}biased} = EV * mbias^{mood(t)} \quad (4)$$

As per Eldar and Niv (2015)'s model, we quantified mood on each trial, $mood_{(t)}$, as the product of mood at the beginning of the trial, $mood_{(t-1)}$, and the RPE on the current trial, $RPE_{(t)}$:

$$mood_{(t)} = mood_{(t-1)} * (1- mrate) + (mrate * RPE_{(t)}) \quad (5)$$

Here, mrate is the mood-update rate, which quantifies how quickly mood is updated from trial-to-trial.

Unlike Eldar and Niv (2015)'s study, we did not use subjective ratings of mood to as a confirmatory check of how well the model captures participants' self-reported mood during the task. However, Eldar and Niv (2015) have confirmed the validity of this model; that it outperformed the standard and other reinforcement-learning models and explained participants' trial-by-trial choices and subjective mood ratings well. Hence, we assume that the model fits well here.

Given that in our task, the probability and magnitude of outcomes were fixed and made explicit in each trial, the RPEs do not have utility for updating expectations. Hence, the choice data in our task was not informative to infer each participant's learning rate, mood-update rate (see below), mood bias parameter (mbias), and mood. Multiple studies have

shown that RPEs are still tracked in tasks with minimal learning components (Rutledge et al., 2017; Rutledge et al., 2014). Given that we cannot infer mrate from our task, we imposed a group-level mrate on all participants, which may not fully capture inter-individual variability. We set mrate to .1, consistent with Eldar and Niv (2015)'s model.

Appendix E: Tests of normality for questionnaire data

Questionnaire	Shapiro-Wilk		Skewness	Kurtosis
	Statistic	*p*-value		
HAMD	0.93	0.16	0.41	-0.92
MAS	0.90	0.03*	0.77	-0.24
MAS log	0.93	0.17	-0.27	-0.97

Note. *Statistically significant $p < .05$; HAMD= Hamilton Depression Rating Scale; MAS= Bech-Rafaelsen Mania Scale; MAS log= log-transformed MAS

Appendix F: Follow-up analyses of the effect of mood symptoms on EV- and RPE-modulated activity in the three regions of interest

Factors	*F*	*df*	*p*
EV			
Ventral striatum			
Main effects			
Laterality	3.12	1, 18	.094
EV	.21	1, 18	.649
HAMD	1.01	1, 18	.329
MAS	2.57	1, 18	.126
Interactions			
Laterality*HAMD	.07	1, 18	.792
Laterality*MAS	5.05	1, 18	.037
EV*HAMD	2.01	1, 18	.174
EV*MAS	1.47	1, 18	.241
Laterality*EV	1.81	1, 18	.196
Laterality*EV*HAMD	.32	1, 18	.577
Laterality*EV*MAS	3.15	1, 18	.093
Anterior insula			
Main effects			
Laterality	.26	1, 18	.616
EV	.40	1, 18	.534
HAMD	6.18	1, 18	.023
MAS	2.02	1, 18	.173
Interactions			
Laterality*HAMD	.35	1, 18	.561
Laterality*MAS	.01	1, 18	.914
EV*HAMD	.02	1, 18	.889
EV*MAS	2.32	1, 18	.145
Laterality*EV	1.53	1, 18	.232
Laterality*EV*HAMD	2.14	1, 18	.161
Laterality*EV*MAS	.66	1, 18	.427
VMPFC			
Main effects			
EV	.17	1, 18	.684
HAMD	1.04	1, 18	.322
MAS	1.10	1, 18	.309
Interactions			
EV*HAMD	1.84	1, 18	.192
EV*MAS	.87	1, 18	.363

RPE

Ventral striatum			
Main effects			
Laterality	.001	1, 18	.973
RPE	1.67	1, 18	.212
HAMD	.25	1, 18	.625
MAS	1.66	1, 18	.214
Interactions			
Laterality*HAMD	.87	1, 18	.363
Laterality*MAS	1.5	1, 18	.237
RPE*HAMD	1.53	1, 18	.232
RPE*MAS	.22	1, 18	.644
Laterality*RPE	.70	1, 18	.415
Laterality*RPE*HAMD	.02	1, 18	.893
Laterality*RPE*MAS	.87	1, 18	.364
Anterior insula			
Main effects			
Laterality	7.77	1, 18	.012
RPE	2.98	1, 18	.102
HAMD	.95	1, 18	.342
MAS	7.49	1, 18	.014
Interactions			
Laterality*HAMD	.31	1, 18	.586
Laterality*MAS	7.41	1, 18	.014
RPE*HAMD	.05	1, 18	.821
RPE*MAS	1.53	1, 18	.232
Laterality*RPE	.58	1, 18	.457
Laterality*RPE*HAMD	3.25	1, 18	.088
Laterality*RPE*MAS	.03	1, 18	.874
VMPFC			
Main effects			
RPE	3.10	1, 18	.095
HAMD	.08	1, 18	.775
MAS	.18	1, 18	.678
Interactions			
RPE*HAMD	.64	1, 18	.433
RPE*MAS	.04	1, 18	.844

Appendix G: Within-group whole-brain activations during anticipation and outcome, at cluster-corrected p< .05 threshold

	Cluster description	k	Peak MNI x	y	z	Brodmann Area	*t*	*p*
Healthy controls								
Standard EV	Right angular gyrus, right supramarginal gyrus	635	34	-62	48	39	5.21	<.001
	Right inferior frontal operculum, right middle frontal gyrus	318	46	12	34	44	4.91	.01
Mood-biased EV	No significant within-group activations							
Standard RPE	Right superior parietal gyrus, right olfactory gyrus, right inferior parietal gyrus	530	32	-64	50	7	6.09	.001
	Right olfactory gyrus, left nucleus accumbens	454	6	14	-8	25	5.20	.001
Mood-biased RPE	No significant within-group activations							
Bipolar disorder								
Standard EV	No significant within-group activations							
Mood-biased EV	No significant within-group activations							
Standard RPE	Bilateral Cuneus	1747	2	-72	18	18	6.35	<.001
	Right nucleus accumbens, right putamen	1608	14	10	-10	-	6.01	<.001
	Left middle temporal gyrus, left angular gyrus	332	-50	-58	20	39	4.59	.006
	Left pregenual anterior cingulate cortex	2445	-10	38	10	-	4.55	<.001
	Left superior frontal gyrus, left middle frontal gyrus	289	-14	34	52	8	4.61	.012

	Right middle frontal gyrus	203	42	18	44	8	4.47	.044
	Right middle cingulate cortex, right supplementary motor area	207	4	4	36	32	4.47	.041
	Left precuneus, bilateral middle cingulate cortex	318	-12	-52	34	32	4.02	.015
Mood-biased RPE	No significant within-group activations							

Note. MNI = Montreal Neurological Institute; EV = expected value; RPE = reward prediction error

Appendix H: Between-group whole-brain activations during anticipation and outcome, p(uncorrected)<.001

			Peak MNI					
	Cluster description	k	x	y	z	Brodmann Area	*t*	*p*
Standard EV HC>BD	Right paracentral lobule, right precentral gyrus, right postcentral gyrus	55	12	-26	68	4	3.82	<.001
Standard EV BD>HC	No significant between-group differences							
Mood-biased EV HC>BD	Left parahippocampal gyrus	8	-26	-28	-22	37	4.06	<.001
Mood-biased EV BD>HC	Left calcarine/precuneus	6	-18	-52	6	30	3.48	.001
Standard RPE HC>BD	No significant between-group differences							
Standard RPE BD>HC	Left precuneus, cuneus	560	-4	-64	20	31	5.74	<.001
	Left middle temporal gyrus	63	-50	-60	18	39	4.05	<.001
	Right supramarginal gyrus	13	64	-48	26	39	4.17	<.001
	Right supplementary motor area	165	8	0	60	6	3.90	<.001
	Left caudate	10	-14	8	10	-	3.83	<.001
	Right angular gyrus	5	42	-62	26	39	3.55	<.001
	Left lingual gyrus	10	-16	-54	0	19	3.54	<.001
	Left superior anterior cingulate cortex	5	0	36	4	-	3.48	<.001
Mood-biased RPE HC>BD	No significant between-group differences							
Mood-biased RPE BD>HC	Right middle occipital gyrus	5	36	-70	38	39	3.71	<.001

Note. EV = expected value; RPE = reward prediction error; HC = healthy controls; BD = bipolar disorder

Appendix I: Modulation of anticipatory and outcome whole-brain activation by depressive and manic symptoms in participants with bipolar disorder, p(uncorrected)< .001

			Peak MNI			
	Cluster description	k	x	y	z	*t*
Negative modulation by depressive symptoms						
Standard EV	Right anterior insula	46	30	22	-6	5.16
	Left caudate	10	-8	14	4	4.08
Mood-biased EV	No significant modulations					
Standard RPE	Left thalamus	7	-10	-10	-2	4.01
	Left precentral gyrus	6	-44	8	32	3.89
	Left retrosplenial cortex	10	-38	-20	-8	3.80
Mood-biased RPE	No significant modulations					
Positive modulation by depressive symptoms						
Standard EV	No significant modulations					
Mood-biased EV	No significant modulations					
Standard RPE	Left parahippocampal gyrus	8	-18	-12	-26	4.39
	Right parahippocampal gyrus	12	12	-8	-22	4.21
Mood-biased RPE	Left nucleus accumbens	5	-4	18	-2	4.01
Negative modulation by manic symptoms						
Standard EV	No significant modulations					
Mood-biased EV	No significant modulations					
Standard RPE	Left and right calcarine	17	0	-58	10	5.32
Mood-biased RPE	Right inferior parietal gyrus	9	54	-44	50	4.07
	Right precuneus	5	14	-50	44	4.02
Positive modulation by manic symptoms						

Standard EV	Right caudate	33	8	10	-2	4.95
Mood-biased EV	No significant modulations					
Standard RPE	No significant modulations					
Mood-biased RPE	No significant modulations					

Note. EV = expected value; RPE = reward prediction error; HC = healthy controls; BD = bipolar disorder