An fMRI Study on the Effects of the Dopamine & Noradrenaline Reuptake Inhibitor Bupropion on Reward Processing in Depressed Individuals

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i. Abstract

Anhedonia, the loss of pleasure or motivation for usually enjoyable activities and rewards, is an established cardinal symptom in Major Depressive Disorder (MDD) whose underlying pathophysiology is not well-understood, and which lacks specific efficacious treatments. This thesis investigates the effects that bupropion, a dual reuptake inhibitor of dopamine and noradrenaline, has on the neural substrates implicated in reward processing amongst clinically depressed individuals compared to unmedicated healthy controls. This investigation may help elucidate the role of aberrant dopaminergic activity on reward processing and the relevance of reward within anhedonia. First, examining baseline neural activation during completion of a monetary reward learning task revealed significantly different functional activity patterns at the whole brain level and for pre-specified anatomical regions of interest in MDD patients compared to healthy volunteers. These activation clusters largely pertained to brain regions implicated in the dopaminergic system, including the striatum, orbitofrontal cortex, and insular cortex. However, this was not found to correlate with symptomatic severity of anhedonia at baseline, which showed significant group differences in anhedonia and positive affect between depressed and healthy control participants.

Administering the NDRI-antidepressant drug bupropion was found to normalise initially aberrant neural activation during reward processing in MDD patients compared to their baseline measures and activation clusters obtained in healthy volunteers. Given the widely reported difficulty in the treatment of reward-related impairments with SSRIs, studying bupropion's effects on neural activation during reward processing contributes to our understanding of alternative therapeutic options for alleviating maladaptive cognition associated with anhedonic MDD aside from those targeting the serotonin system. The gained insights may thus help inform the development and implementation of more precise and efficacious pharmacological interventions used for treating symptoms of anhedonia in clinical depression. Methodological strengths as well as possible limitations to the findings obtained in this study are discussed.

ii. CONTENTS

CHAPTER 1: RESEARCH BACKGROUND

CHAPTER 2: METHODOLOGY

CHAPTER 3: BASELINE DIFFERENCES

CHAPTER 4: GROUP DIFFERENCES AFTER BUPROPION TREATMENT

CHAPTER 5: GENERAL DISCUSSION

iii. Acknowledgements

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iv. Declaration

The data analysed as part of this MSc (by Research) project was collected by Dr Annabel Walsh, a former DPhil student at the Department of Psychiatry under the supervision of Professors Catherine Harmer and Michael Browning. I declare that all analyses reported in this thesis were performed by myself, and that the write-up does not exceed the maximum word limit set for MSc (by Research) theses.

v. Abbreviations

ACC – Anterior cingulate cortex

BAT – Behavioural activation therapy

BET – Brain extraction tool

BMI – Body mass index

BOLD response – Blood oxygen level-dependent response

CBT – Cognitive behavioural therapy

DA – Dopamine

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition

EPI – Echo planar image

EV – Explanatory variable

fMRI – Functional magnetic resonance imaging

FMRIB – Functional magnetic resonance imaging of the brain

FSL – FMRIB Software library

GLM – General linear model

HC – Healthy controls

HRF – Haemodynamic Response Function

IQ – Intelligence quotient

MDD – Major depressive disorder

MNI – Montréal Neurological Institute

NA – Noradrenaline

NAcc – Nucleus accumbens

NART – National adult reading test

NDRI – Noradrenaline-dopamine reuptake inhibitor

OFC – Orbitofrontal cortex

PANAS – Positive and Negative Affect Schedule

PFC – Prefrontal cortex

PILT – Probabilistic instrumental learning task

ROI – Region of interest

RPE – Reward prediction error

SCID – Structured Clinical Interview for DSM-IV

SHAPS – Snaith-Hamilton Anhedonia Pleasure Scale

SNRI – Serotonin-noradrenaline reuptake inhibitor

SSRI – Selective serotonin reuptake inhibitor

SVC – Small volume correction

TE – Echo time

TR – Repetition time

vm – Ventromedial

VS – Ventral striatum

VTA – Ventral tegmental area

Chapter 1:

Research background

Anhedonia, the loss of pleasure or motivation for usually enjoyable activities and rewards, is an established cardinal symptom in Major Depressive Disorder (MDD) whose underlying pathophysiology and efficacious clinical treatments are not well-understood. This thesis investigates the effects that bupropion, a dual reuptake inhibitor of dopamine and noradrenaline, has on the neural substrates implicated in reward processing amongst clinically depressed individuals compared to unmedicated healthy controls. Administering this antidepressant drug may help elucidate the role of aberrant dopaminergic activity on reward processing and the relevancy of reward within anhedonia. Studying bupropion's effects on neural activation during a reward learning task will contribute to our understanding of the neurobiological anomalies that underpin maladaptive cognition associated with anhedonic MDD. The gained insights may help inform the development and implementation of more precise and efficacious pharmacological interventions used for treating symptoms of anhedonia in clinical depression.

1.1. Aetiology of Major Depressive Disorder

The aetiology of Major Depressive Disorder (MDD; also unipolar depression) is complex and associated with a myriad of different factors. These are largely rooted in environmental processes as well as genetic variations which can induce structural and functional abnormalities in the brain, and influence the incidence of neuropsychiatric illnesses (Bohacek et al., 2013; Thompson et al., 2001; Guintivano & Kaminsky, 2016). Correspondingly, data obtained from twin studies has evidenced the strong genetic basis of both main categories of mood disorders, namely bipolar disorder and MDD, albeit with a greater heritability for bipolar disorder (Wray & Gottesman, 2012). However, concordance rates, even in monozygotic twins raised in the

same household, do not approximate 100%, hence highlighting the importance of epigenetic and environmental factors. Prenatal exposure to excessively elevated glucocorticoid levels, a biomarker of heightened HPA activity and stress, has been found to modulate offspring's cortisol concentration (O'Connor et al., 2013; Bolten et al., 2013). This increases infants' vulnerability to developing MDD as stress itself is implicated in the risk of affective dysregulation and anhedonia (Henn & Vollmayr, 2005; Bale, 2006; Pizzagalli, 2014). Nolvi et al. (2016) illustrated the epigenetic link between stress and negative emotionality by showing that children whose mothers reported greater prenatal stress tended to score higher on measures of negative emotional reactivity. Although mothers' recall and report biases cannot be ruled out, the prenatal "programming" of infants' stress sensitivity and the implications for negatively biased information processing are robustly supported by the literature (Essex et al., 2002; Möhler et al., 2006; Davis et al., 2011; Davis et al., 2020). Furthermore, adverse life events such as childhood trauma, abuse, and poverty have been identified as risk factors contributing to psychiatric and specifically affective illness (Yoshikawa et al., 2012; Hayashi et al., 2015; Palacios-Barrios & Hanson, 2019). In summary, these, amongst other (quasi-)environmental factors, interact with individuals' genetic susceptibility to mood disorders, and additionally influence their cognition, behaviour, and personality.

Given the widespread occurrence of various kinds of childhood adversity as well as the frequency of environmental stress and hardship, it is not surprising that the prevalence and health burden of depression, personally and economically, is immense. According to the World Health Organization (WHO; 2017), it is estimated that over 300 million individuals worldwide suffer from MDD, indicating annually rising incidence (James et al., 2018). This emphasises the pressing need for improved therapeutic interventions, including psychopharmacological tools, that can alleviate the devastating impact of mood disorders like MDD. A critical step towards doing so is better understanding the symptomatic, cognitive, and neurobiological mechanisms underlying anhedonia to inform the development of effective treatments.

1.2. Terminology & Cardinal Symptoms in Major Depression

Psychiatric symptoms of MDD can manifest themselves differently throughout patients' trajectory of illness in addition to inter-individual variation (Judd et al., 1998; Ferro et al., 2015; Cole et al., 2002). Clinical depression is particularly characterised by anhedonia, the diminished or absent ability to derive pleasure from previously enjoyable experiences (i.e., decreased positive affect), and low/depressed mood (i.e., increased negative affect; Ribot, 1897; Leventhal et al., 2006; Loas et al., 1994). Although clinically low mood and diminished pleasure, alongside loss of motivation, are the main pillars warranting a diagnosis of MDD, it is critical to emphasise that both comprise far-reaching phenomena. Correspondingly, persistent low affect is not limited to sadness alone but can go as far as triggering profound hopelessness, if not suicidality (Wetzel, 1976). Many sufferers report losing their sense of purpose as they carry the burden of being unable to engage with loved ones, and changes in libido and appetite (Ge et al., 2017; Casper et al., 1985). This relates to the insidious impact of anhedonia as well, which may present itself despite no acute feelings of 'depressiveness' per se (Heininga et al., 2017).

Importantly, reducing the disabling and negative feelings, thereby treating the "depressed mood" MDD is associated with, does not automatically ameliorate anhedonia (Hoehn-Saric et al., 1990). Whilst the symptomatic distinction arguably highlights the heterogeneity of "*the* depressed phenotype", it has pivotal implications for patient treatment, too. Accordingly, it is worth mentioning that symptoms of low mood and anhedonia respectively are thought to be underpinned by different neurotransmitter systems (Nutt et al., 2007; Hamon & Blier, 2013; see Section 1.5.). Therefore, differential psychopharmacological treatments are suggested to appropriately address the complex behavioural and emotional difficulties an individual may be facing. Conversely, antidepressant prescriptions that do not consider the neural mechanisms underlying either symptomatic cluster may fail to sufficiently support concurrent interventions, such as cognitive therapies (DeRubeis et al., 2008; Delgado, 2004).

1.3. Treatment Approaches for MDD

The neuropsychological anomalies that are widely associated with MDD include negative biases in the attention to, as well as perception, appraisal, and recall of emotional stimuli (Gotlib et al., 2004; Lawson & MacLeod, 1999; Wisco & Nolen-Hoeksema, 2010; Ridout et al., 2003; Kuyken & Dalgleish, 1995). A key cognitive model of depression addressing this negatively biased information processing was introduced by Beck in 1967. According to this framework, depressed patients hold pessimistic views of themselves, their experience of the world, and their future. Being also referred to as the "cognitive triad of depression", Beck's model helps explain the persistence of MDD. If individuals repeatedly encounter failure due to depressed mood and lack of motivation, they may ascribe said failure to their low personal worth (Roberts & Monroe, 1994; Liu & Huang, 2018). This might then prompt pessimistic beliefs about one's prospects (Sokol & Serper, 2017). Thus, if a negative outlook on one's future is upheld, patients are susceptible to thinking that "everything is bad", which amplifies self-blame further, and perpetuates a vicious circle of depressed mood (Teasdale, 1988; Williams et al., 1990). These dysfunctional cognitive patterns outline the theoretical basis for Cognitive Behavioural Therapy (CBT) wherein patients address their maladaptive thought processes by critically appraising them (Garratt et al., 2007; McGinn, 2000). This aims to facilitate a more realistic, potentially positive, view of themselves, the world, and their future, hence alleviating symptoms of MDD (Hoffart & Sexton, 2002).

1.3.1. The Importance of Addressing Motivational Deficits

Importantly, traditional psychotherapies may fail to adequately accommodate patients' condition if the treatment focus lies solely on emotion dysregulation without acknowledging symptoms of anhedonia. Anhedonic individuals tend to report a lack of positive experiences, corresponding to a decrease in positively valent affect (Werner-Seidler et al., 2014). In order to resolve this, cognitive therapies have been implementing Behavioural Activation Therapy

(BAT), a strategy that encourages patients to deliberately seek out pleasurable/rewarding activities (Dimidjian et al., 2011; Dimidjian et al., 2014). Its efficacy in treating MDD more generally has been argued similar to that of CBT, yet, Behavioural Activation would address the cardinal cluster of anhedonia more specifically than CBT alone (Mazzucchelli et al., 2009). Such clinically significant improvements of anhedonia thanks to BAT appear to pertain to virtual reality, too. Importantly, investing in digital aids for therapeutic purposes would help address some of the barriers to accessing crucial mental health care in-person, an issue that has become increasingly problematic.

Watson et al. (2021) also found positive effects on participants' self-reported anhedonia after implementing BAT strategies, albeit limited in cases of particularly high symptomatic severity. This somewhat variable responsiveness to BAT for depression may be influenced by individuals' environmental circumstances in that affected individuals may feel too burdened to actively engage with positive activities (Aoki et al., 2021). This pronounced lack of motivation may consequently compromise the effectiveness of BAT, warranting a greater level of psychiatric attention and support.

Despite some varying results concerning its clinical efficacy depending on symptom severity, BAT may indeed offer a much-needed tool in supporting patients' capacity to engage in pleasurable activities (Cuijpers et al., 2007; Chartier & Provencher, 2013; Ekers et al., 2014). Facilitating those positive experiences by means of a bottom-up approach may then help alleviate symptoms of anhedonia and improve patients' subjective well-being. Nonetheless, it is crucial to acknowledge that clinical depression, including anhedonic symptomatology, is an illness whose behavioural features have a strong biological basis. Correspondingly, neuropsychiatric research has expounded how cognitive and behavioural impairments in anhedonic patients pertain to differences in the anatomy, activity, and function of the dopaminergic system.

1.4. The Neurobiology of Reward Processing

The brain's reward circuitry comprises both higher cortical regions, such as the prefrontal (PFC) and orbitofrontal cortices (OFC), as well as limbic structures, including the ventral tegmental area (VTA), striatum, amygdala, and hippocampus. That this network, collectively referred to as the mesocorticolimbic pathway, is implicated in symptoms of anhedonia was first postulated by Wise (1982). Earlier theories of reward like the Drive Theory (Hull, 1943) had argued that reward acted to reduce 'drive', the homeostatic mechanisms instigating behaviour to occur (e.g., "primary rewards"; food, access to sexual mates). However, this proposal contrasted with findings by Olds and Milner (1954) who showed that rats engaged in intracranial self-stimulation of brain regions high in dopaminergic neuron density by pressing a lever despite no biological 'drive' to do so. Instead, these findings allude to a rewarding effect in and of itself beyond mere homeostatic regulation. Additional support was provided by intravenous and intragastric feeding experiments. For instance, Miller and Kessen (1952) demonstrated that rats that were given milk intragastrically ran slower in a T maze to obtain the milk reward than those who received it orally. The speed of running was thus determined by the *experience* of the reward as the drive, hunger, itself, had been reduced in both conditions. These observations prompted further investigation into the neurobiology of reward and revealed that administering psychotropic agents that enhanced dopamine signalling, like pimozide, ensued an increase in reward-eliciting behaviours (Yokel & Wise, 1975). Conversely, lesioning brain regions such as the OFC and ventral striatum (VS) ensued impairments in reward-related behaviour (Cooch et al., 2015). Specialist techniques such as functional neuroimaging and electrophysiological recordings further corroborated the link between the brain's dopaminergic circuitry and reward (Liu et al., 2011; Schultz et al., 1992).

1.4.1. The Anhedonia Hypothesis

Wise's 'Anhedonia Hypothesis' (1982) was based on the observation that administering neuroleptics in rats, hence blocking the release of dopamine, ostensibly impaired their pleasurable experience of rewarding stimuli (Wise et al., 1978). This was suggested by a marked decrease in the animals' food intake, their effort to obtain the food, and instrumental responding. In an application to psychiatry, Wise's theory would posit that anhedonic patients are impaired in their ability to experience pleasure as a function of aberrant dopamine signalling. Yet, the experimental evidence indicates that symptoms of anhedonia are not limited to the hedonic impact of an experience. Rewards have been subsequently described as any stimulus, object, event, or activity that acts as a positive reinforcer due to its incentive properties (Anselme, 2009; Schultz, 2015). Accordingly, rewards elicit feelings of pleasure and can prompt the desire to *approach* rewarding stimuli. This suggests that the behaviour observed by Wise, amongst others, would not be solely attributable to the supposedly pleasurable experience of a reward itself ('consummation'), but also the anticipation thereof. Hence, it has been noted that dopaminergic activity can be modulated by the mere presentation of a reward-signalling stimulus, predicting its occurrence, and thereby incentivising the individual to pursue it.

1.4.2. Anticipation versus Consummation of Reward

The distinction between anticipation and consummation of a reward, including their dopaminergic signatures, is note-worthy as these point towards the computations that occur to facilitate learning (Schultz & Dickinson, 2000). The difference between an expected outcome of a reward-signalling stimulus based on prior experience (anticipation) and the actual outcome (consummation) is termed 'reward prediction error' (RPE). These behavioural prediction errors are underpinned by neural mechanisms. Schultz et al. (1997) recorded single-cell activity of dopaminergic midbrain neurons in monkeys when they were presented with different rewarding stimuli. Prediction error responses are supported by dopaminergic neurons, indicated by short

phasic bursts of activity after receipt of an unpredicted reward. When primates were presented with a cue predicting the reward, neural activity shifted from post-reward to the time of cue onset as the cue elicited a prediction error. This shift in phasic activity in anticipation of the reward also reflects that dopamine is involved in motivational behaviour, or 'wanting'. When predicted rewards were omitted, dopaminergic activity at the time of expected reward receipt reduced relative to baseline. This illustrated the neurobiological basis of negative RPE and showed that dopaminergic neurons also encode the omission of expected rewards (Tobler et al., 2003).

1.4.3. The Incentive Salience Hypothesis

The importance of reward anticipation alludes to the conceptual basis of the 'Incentive Salience' hypothesis, introduced by Berridge & Robinson (1998), and raising additional rebuttal to Wise's Anhedonia Hypothesis. They lesioned rats' substantia nigra, a midbrain structure high in dopamine, with *6-hydroxydopamine* (6-OHDA) and found that doing so significantly reduced the effort animals were willing to exert to acquire food. However, hedonic responses, as indicated by lip smacking, were not decreased. They thus concluded that the evidence would not necessarily support a link between dopamine and the hedonic experience ('liking') of a pleasurable stimulus per se. Instead, it was argued that 'liking' responses had been erroneously inferred from measures of 'wanting', i.e., the motivational incentive to seek out a reward-signalling stimulus. This corresponds to Peciña et al. (1997) who had previously observed no change in hedonic responding to food in rats despite the administration of neuroleptics. Moreover, it has been shown that DAT (dopamine transporter) knockout in mice increased their food intake as well as running to food locations without modifying reactions to food consumption (Peciña et al., 2003; Cagniard et al., 2006). Similarly, Wyvell and Berridge (2000) found that administering amphetamine to rats' nucleus accumbens, thereby increasing dopaminergic signalling, did increase lever pressing to obtain food (anticipatory, motivational

behaviour) whilst not affecting hedonic, consummatory responses. Collectively, these results suggest a dissociation between the neural underpinnings of the consummation or experience of a rewarding outcome and the anticipatory, appetitive behaviour instigating its pursuit.

Corresponding to the salience hypothesis of dopamine, it has been posited that mesolimbic neurons also respond to aversive stimuli (Horvitz, 2000). Accordingly, the responding to both appetitive, pleasurable stimuli and unpleasant ones would guide attention and behaviour. However, evidence obtained by Ungless et al. (2004) instead suggests that midbrain neurons that respond to aversive stimuli are not dopaminergic per se as DA neurons are supposed to respond to aversive events with a reduction in firing. According to Schultz (2016), initial DA neural activation reflects the salience of events so that neurons must respond to aversive and appetitive information to facilitate learning. Thereafter, larger responses in dopaminergic neurons indicate a reward response that is elicited for appetitive events. In support of the role of dopamine in incentive salience, Chow et al. (2016) found that DA lesions in the nucleus accumbens impaired sign-tracking without altering goal-tracking in rats. This suggests a dissociation between incentive salience (anticipatory attention paid to reward-signalling stimuli) and RPE, which computes the difference between expected and actual outcome. Moreover, they observed that inhibition of D_1 and D_2 receptors differentially impacted rats' acquisition of incentive salience (anticipation) whereby inhibiting D_1 receptors specifically compromised learning. These results foster the notion that different components of reward processing are underpinned by dissociable neural systems and structures which collectively constitute the dopaminergic circuitry of the brain.

1.4.4. Reward Prediction Error in Humans

Functional MRI has subsequently been used to investigate the neural correlates of prediction errors in humans. For instance, Abler et al. (2006) presented healthy volunteers with a cue informing them about the probability of receiving monetary rewards for correct responses and

measured neural activation during probability cue onset and reward response. Nucleus accumbens responding reflected primate dopaminergic neural phasic activity (Schultz et al., 1997; Schultz, 2000), as responding to cues increased linearly with the expectation of reward, but responses to reward outcomes decreased linearly with expectation of reward. Omitted rewards were coded as negative prediction errors and resulted in a larger negative response relative to baseline activity. Furthermore, fMRI measures taken during either the expectation or consummation of a monetary reward in healthy human participants have revealed reward anticipation as being underpinned by ventral striatal activity, thus encoding the predictability of reward (Knutson et al., 2001; McClure et al., 2003). Conversely, reward outcomes elicited the greatest neural response in the ventromedial frontal cortex. This indicates that separable neural systems integrate reward-related information and drive behaviour so that decision-making can maximise reward.

1.4.5. The Neural Substrates of Reward Processing

With regards to the present study design, it is worth noting that primary and secondary rewards are processed differently, including dissociable neural substrates (Sescousse et al., 2013). Primary rewards serve homeostatic, physiological, or reproductive functions (e.g., food, sex) whereas secondary rewards (e.g., money) serve to enhance the function of primary rewards. Primary rewards are inherently unconditioned as they do not rely on behavioural reinforcement and are carried out for the sake of survival. In contrast, secondary rewards are predominantly conditioned as these stimuli are learnt to be associated through experience. Affective processing of reward, alluding to motivational behaviour/'wanting' predominantly occurs in sub-cortical brain regions, such as the striatum. To assign value to rewarding stimuli, especially more abstract information, and secondary rewards, such as monetary cues, however, requires cognitive computations to prompt appropriate decision-making (Peters & Büchel, 2010). This neural representation of reward has been linked to higher cortical, prefrontal regions, most

prominently the orbitofrontal cortex (OFC). The OFC receives somatosensory, olfactory, and visual inputs to then reinforce behaviour via top-down processing (Rolls, 2000; 2016). As shown by single-cell recordings in primates, prefrontal activation when tasting glucose is reduced once satiety had been achieved whilst responses in the primary gustatory cortex are sustained (Rolls, 1989). This suggests orbitofrontal encoding of reward value specifically and the OFC's role in incentive by updating stimulus-reward associations depending on reward contingencies (Klein-Flügge et al., 2013; Rudebeck et al., 2009).

The OFC has hence been associated with representing goal and decision values whilst the VS provides input to compute prediction errors and assist learning (Hare et al. 2008; Daniel & Pollmann, 2014). Said value representation appears to be largely modulated by medial portions of the OFC and is relative, rather than absolute, thus emphasising the subjective nature of (secondary) reward processing (Elliot et al., 2008). Importantly, medial orbitofrontal responding is thought to underpin the anticipation of positive reward and corresponding decision-making, with the lateral divisions of the OFC being more implicated in reward learning (Knutson et al., 2001; McCabe et al., 2012; Liu et al., 2011). Additionally, the processing and encoding of negative prediction error in terms of aversive (affective) information/risk has been related to the anterior insular cortex (Garrison et al., 2013; Knutson & Bossaerts, 2007). A quantitative voxel-wise meta-analysis conducted by Mohr et al. (2010) revealed robust activation of the anterior insula in response to high-probability loss scenarios. This pattern was obtained for both, anticipation of punishment as well as decision-making with high levels of uncertainty, hence indicating risk of aversive outcomes. Conversely, anterior insular lesions have been shown to impair punishment-based avoidance behaviour (Palminteri et al., 2012). Recent evidence also demonstrates connectivity and co-activity between anterior insula and medial OFC as critical modulators of successful reward processing and learning in that insular signals relayed performance feedback on prior errors to the mOFC (Billeke et al., 2020).

Anterior insular activation was significantly correlated with subsequent task accuracy and thus corroborates its role in negative reward and risk prediction, and helps describe the neural mechanism whereby loss anticipation occurs. This further elucidates the neurobiological basis of reward processing and illustrates the dissociable, yet interconnected, roles of different components of the dopamine system in the integration of reward-related information.

A dissociation between anticipatory/appetitive and consummatory/hedonic responding to reward in humans has been widely studied in clinical populations, too. For instance, Sienkiewicz-Jarosz et al. (2013) reported atypical 'wanting' responses amongst patients suffering from Parkinson's disease (PD) whilst hedonic responses remained unimpaired. As PD is marked by atrophy of the dopaminergic system, their results foster that dopamine's role in reward processing concerns motivation-based, goal-directed behaviour. PET measures obtained by Kasanova et al. (2017) from healthy participants have further emphasised and elucidated the role of striatal dopamine in differential strength of motivation. They observed widespread dopaminergic activation in response to rewards as subjects performed a reinforcement learning task. Importantly, dopaminergic activity in the right caudate and nucleus accumbens specifically was significantly correlated with individuals' tendency to display reward-related behaviours and their motivation to seek out rewarding activities.

1.4.6. The Pathophysiology of Anhedonic MDD

Notably, these data also translate to the behavioural pathology seen in some clinically depressed individuals as unmedicated depressed patients were marked by reduced caudate and nucleus accumbens activity compared to healthy individuals (Pizzagalli et al., 2009). More distinctly, decreased functional connectivity of the nucleus accumbens sub-divisions as measured by fMRI has been found to positively correlate with greater severity of anhedonic symptoms (Liu et al., 2021). According to Schlaepfer et al. (2008), applying deep brain stimulation to the nucleus accumbens, being high in dopaminergic neurons, alleviated symptoms of anhedonia in

depressed patients. Despite the limited sample size (N=3), these observations may point towards promising avenues for developing treatments for anhedonic MDD. Additionally, they further validate the link between impaired reward processing being underpinned by aberrant dopaminergic functioning and corroborate the relevance to anhedonia in major depression. They thus align with prior evidence suggesting both a reduction in accumbens activity and volume as neurological driving factors of anhedonia and aberrant reward reactivity (Wacker et al., 2009; Carlson et al., 2015).

Furthermore, blunted RPE responses have also been associated with disrupted functional connectivity between the striatum and habenula. Accordingly, the striatum receives feedback from the habenula, a structure related to the encoding of negative RPE, or punishment/loss (Salas et al., 2010). If habenular activity is dysregulated and can neither encode nor relay aversive information appropriately to striatal regions involved in reward learning and risk avoidance, impairments in reward anticipation are likely more pronounced (Matsumoto & Hikosaka, 2007; Proulx et al., 2014). This has been supported by observing poorer performance on a monetary learning task in unmedicated depressed patients who displayed aberrant functional striatal-habenular connectivity (Kumar et al., 2018). Their greater difficulty to optimise decision-making by learning to avoid negative cues as a function of abnormal connectivity also relates to symptoms implicated in anhedonia. Correspondingly, Liu et al. (2017) found habenular dysfunction to be positively correlated with motivational impairments in depressed individuals. This aligns with habenular functional connectivity as a significant predictor of treatment response in MDD, with a reduction being a biomarker of treatment-resistant depression (Gosnell et al., 2019).

Given the large-scale integration of information to promote reward learning and decision-making, it is not surprising that habenular projections also reach the OFC. Aversive, loss-related responses from the lateral habenula would thereby be relayed to prefrontal regions to facilitate

more accurate computations regarding potential outcomes and reward-conducive behaviour (Rolls, 2017). Conversely, decreased orbitofrontal activation during loss scenarios has been positively correlated with greater severity of MDD symptoms and a poorer trajectory of the illness, the latter being independent of patients' current clinical condition (Jin et al., 2017). Moreover, the same study found increased connectivity between OFC and insula as a significant predictor of future depressive symptomatology. This emphasises the impaired encoding of negative prediction error responses, driven by aberrant insular and habenular function, as additional mechanistic correlates of the biology underlying anhedonic MDD.

The large-scale network underlying depression further extends to ventromedial prefrontal areas of the brain, reiterating the neural distinction between MDD per se and anhedonia. This has been demonstrated by monitoring neural responses to positive (happy) stimuli via fMRI in depressed patients with varying degrees of anhedonia (Keedwell et al., 2005). All depressed participants reported mood changes corresponding to the presented emotive stimuli. However, only those with marked anhedonia showed heightened activity in the ventromedial prefrontal cortex (vmPFC), the structure associated with a neural representation of reward (Bartra et al., 2013). Conversely, individuals indicating no or low anhedonia did not show this neural pattern. Thus, aberrant vmPFC activity may impinge on anhedonic subjects' cognitive appraisal and integration of rewarding stimuli, and consequently require greater effort than neurotypical controls would exert.

Moreover, the depressed subjects with impaired reward processing tested by Keedwell et al. (2005) simultaneously displayed blunted activity in striatal regions. The striatum is high in dopaminergic neuron and receptor density so that reduced activity thereof aligns with individuals' diminished ability to process reward, contributing to symptoms of anhedonia in MDD (Berridge & Kringelbach, 2015; Admon & Pizzagalli, 2015). Heller et al. (2009) exposed depressed individuals to positively valent images and observed significantly diminished ability

to maintain engagement compared to healthy controls, corresponding to lower self-reported positive affect. They found the reduced capacity for sustaining positive emotions to be underpinned by aberrant fronto-striatal network connectivity measured over the course of the task, especially involving the nucleus accumbens. Similarly, pharmacologically enhancing sustained nucleus accumbens activity and connectivity to frontal brain regions proportionally improved MDD patients' self-reported positive affect (Heller et al., 2013). These results emphasise the fronto-striatal network as a therapeutic target for treating anhedonic depression, both on a neural level and in terms of clinical symptoms. The cognitive and behavioural traits associated with this network further allude to possible avenues for experimentally assessing and subsequently treating anhedonia, too, as will be discussed shortly.

Notably, increased vmPFC activity upon exposure to positive emotional stimuli in correlation with lower hedonic capacity has also been obtained from a non-clinical sample (Harvey et al., 2007). Meanwhile, the basal ganglia were markedly reduced in size in those participants with greater trait anhedonia. These findings illustrate a distinct neurological endophenotype modulating individual differences in anhedonia beyond the realms of clinical depression (Hasler et al., 2004; Pizzagalli, 2014). Accordingly, low reward capacity may serve as a qualitative, premorbid indicator of susceptibility, potentially allowing early intervention utilising behavioural and cognitive approaches (Craske et al., 2016).

Furthermore, recovery from anhedonic MDD may allow subjective improvements in clinical symptoms, yet, recovered individuals' neural representation of rewarding stimuli remains abnormal. When McCabe et al. (2009) exposed remitted, unmedicated MDD patients to pleasurable or aversive stimuli, doing so did not elicit differential neural responses in the primary gustatory cortex compared to healthy controls. However, MDD subjects displayed significantly decreased activation of brain regions implicated in processing appetitive information, including the ventral striatum when viewing and tasting the pleasurable stimuli,

such as chocolate and strawberries. This observation demonstrates that, although the sensory perception of the presented stimuli was intact amongst patient participants, their impairment was of an integratory nature. Accordingly, stimuli such as chocolate, being perceived as positive on a sensory level, were neurally represented as less rewarding, aligning with the diminished motivational response that characterises anhedonic MDD.

Whilst ventral striatal hypoactivity had also been shown in present MDD sufferers (Epstein et al., 2006), replicating the results in ostensibly recovered individuals corroborates the evidence around anhedonia as a trait vulnerability marker within and beyond acute depression. Neurobiologically, too, anhedonia is hence revealed as a clinical feature both predisposing individuals to MDD, in addition to underscoring anhedonic symptomatology as a life-time risk factor for recurring depression (Eaton et al., 2008). Notably, Dichter et al. (2010) found that depressed individuals omitting symptoms of clinical anhedonia do not report phenomenological differences in response to sweet taste compared to healthy participants. This fosters the notion that anhedonia is a cardinal cluster independent of major depression in addition to supporting the link between anhedonia and reward processing specifically (Fawcett et al., 1983; Hasler et al., 2004). Moreover, Salvadore et al. (2011) observed that formerly depressed individuals who had been in prolonged remission did not significantly differ in prefrontal anatomy when compared to healthy controls. Currently depressed participants, however, did display characteristic structural alterations such as reduced prefrontal grey matter volume and density. This suggests a differential role of prefrontal structure versus striatal functional activity, respectively, as possible long-term risk markers beyond remission from (anhedonic) MDD. These results hence emphasise the need to investigate the mechanistic factors underlying MDD psychopathology, the distinct role of anhedonia, as well as its implications and relevancy to clinical practice.

1.4.7. Assessing Anhedonia Experimentally & the Role of Motivation

The aforementioned behavioural and neural features have to be accounted for when developing accurate and methodologically sound tools for assessing anhedonia experimentally. Given the discussed link between incentive salience and anticipatory behaviour, it is arguably most relevant to apply measures that test motivation, such being characteristically impaired in anhedonic MDD. Treadway et al. (2012) developed the 'Effort Expenditure for Rewards Task' (EEfRT), conceptually analogous to Berridge & Robinson's animal model of dopamine-depleted lack of effort expenditure in rats despite hedonic responding. Over the course of various trials, participants were given the choice as to whether they would like to exert greater effort (motivation) for the chance to gain larger amounts of money. Theoretically, anhedonic subjects would be expected to display diminished capacity or willingness to exert effort for obtaining greater rewards, hence indicating elevated levels of anhedonia. Experimental findings confirmed this hypothesis, in addition to showing that depressed individuals were also impaired in their ability to use the reward-related information to optimise subsequent decision-making. The latter was found to be positively correlated with participants' self-reported anhedonia and further pertained to remitted MDD sufferers as well as healthy volunteers (Yang et al., 2014). This proposes monetary incentive paradigms as useful tools for monitoring reward-related behaviour in MDD patients, with deficits being suggestive of underlying anhedonia. Moreover, it reiterates the cardinal cluster of anhedonia and its symptomatic variability within and beyond the realms of major depression.

Importantly, hedonic processing may also relate to anticipatory appraisal of reward, hence being a more heterogenous construct than often thought. Sherdell et al. (2012) compared healthy volunteers and depressed patients on a motivation-based task to assess effort expenditure for rewarding stimuli. Despite no group differences in consummatory responding overall, 'liking' the stimuli was only a determining factor amongst healthy controls when deciding whether to expend effort for obtaining the reward. In depressed participants, however, their degree of *anticipatory* pleasure was a significant predictor of subsequent motivation to seek out rewards.

Chiefly, individual variation in anhedonia levels within the MDD patient group correlated with impaired task performance and reduced effort expenditure. These results foster the dissociation between consummation and anticipation in anhedonia. They also assert that motivational impairments in MDD are specifically modulated by diminished anticipatory pleasure, aligning with the established notion of anhedonia. Consequently, anhedonic individuals seemingly demonstrate a lack of motivation due to lower *expectations* of the pleasure they might derive from experiencing the rewarding stimuli, rather than the experiential, consummatory pleasure itself (Geaney et al., 2015).

It has hence been noted that assessing anhedonia experimentally may be superior and more clinically relevant than using self-report questionnaires alone – this is suggested not only by the historical emphasis on negative affect in MDD diagnosis, thus potential failure to measure anhedonic symptoms specifically (Rizvi et al., 2016). Task performance may also permit insights into the nuances of behavioural differences in depressed individuals which questionnaires are liable to neglect. Besides, using validated behavioural paradigms for assessing anhedonia instead better aligns with an increasingly recognised transdiagnostic approach whereby anhedonia and aberrant reward processing are acknowledged beyond major depression (Nusslock & Alloy, 2017).

1.4.8. *Aberrant Reward Processing & Diagnosing Anhedonia in MDD* – Interim summary

The research literature therefore illustrates the role of dopamine in aberrant reward processing and corroborates its implications for anhedonia as a therapeutic target for treating clinical depression. Given the discussed pathophysiological correlates, it often does not suffice to limit patient treatment to cognitive therapies to achieve significant improvements in symptoms and overall well-being. Consequently, additional support through antidepressant treatment may be needed to adequately help patients engage with psychotherapies by addressing their supposedly disrupted neurochemistry, too. Possible mechanisms of this, which are assumed to be dysregulated in MDD sufferers, will be discussed in following sections of this chapter.

1.5. Neurochemical Dysfunction in MDD

A prominent theory of the underlying mechanism of MDD, amongst related mood disorders, is the monoamine hypothesis, postulating that clinical symptoms depend upon monoaminergic dysfunction in the brain (Stahl, 1998). The hypothesis predominantly focusses on three key neurotransmitters, namely serotonin, noradrenaline, and dopamine, and their respective neurochemical effects. This assumption originates from clinical observations showing that depressed individuals are marked by abnormal concentration of these neurotransmitters (Cowen, 2008). Conversely, establishing 'normal' levels of these monoamines by administering pharmacological agents has been found to alleviate cognitive and behavioural symptoms associated with depression.

1.5.1. Noradrenaline & Serotonin in Mood Regulation

Alongside serotonin, noradrenaline has also been demonstrated to crucially underpin affective dysregulation in MDD (Ressler & Nemeroff, 1999). Outhred et al. (2013) conducted a meta-analysis of fMRI studies to investigate the neural activation patterns underpinning serotonergic and noradrenergic antidepressant treatment, respectively. Neural effects of SSRI drug administration were predominantly marked by changes in amygdalar function, corresponding to prior findings showing normalised threat perception as a correlate of reduced amygdalar activity in SSRI-treated subjects (Godlewska et al., 2012; Murphy et al., 2009). Acute inhibition of noradrenaline reuptake, on the other hand, increased frontal activity in response to emotive stimuli, indicating enhanced ability for higher cognitive regulation. These results imply differential therapeutic effects of SSRI and NRI drug treatment on emotional processing. Accordingly, serotonin may support a more limbic, bottom-up normalisation of brain activity and thereby correct the aberrant sensitivity to emotional information seen in MDD. Meanwhile, noradrenaline reuptake inhibition may enable an adaptive perception of affective stimuli via relatively greater effects on enhanced top-down, prefrontal processing

compared to SSRIs (Harmer et al., 2011; Roiser et al., 2012). For treating mood-related impairments associated with major depression such as increased negative affect, these insights support the use of combined serotonin-noradrenaline reuptake inhibitors to maximise clinical efficacy (Stahl et al., 2005; Thase et al., 2008). However, further investigation into potentially differential neuropsychological effects of serotonin and noradrenaline reuptake inhibition is needed to substantiate these preliminary conclusions.

Many conventionally prescribed antidepressants are thought to lack specificity in treating anhedonia in depression due their mechanism of action. For example, SSRIs selectively inhibit the reuptake of serotonin, the neuromodulator more prominently associated with ameliorating emotion processing in mood disorders. SSRI treatment has hence been shown to improve negative attentional and recognition biases of fearful or sad faces in individuals with a history of MDD as well as healthy volunteers, albeit with initial deterioration of symptoms upon drug administration (Harmer et al., 2009; Bhagwagar et al., 2004; Browning et al., 2007). Additionally, antidepressant drugs targeting serotonin have yielded normalisation of the functional activity of brain regions implicated in emotion dysregulation (Godlewska et al., 2012; Young et al., 2020), however, with few, or negative effects on neural correlates of reward processing (Abler et al., 2012; Macoveanu et al., 2014; McCabe et al., 2010). These findings have been obtained in both healthy and clinically depressed samples and help explain the commonly reported side-effects of emotional blunting under SSRI drug treatment. Accordingly, targeting serotonin as a first-line treatment for MDD is potentially myopic precisely due to the heterogeneity of the illness and anhedonia being a cardinal symptom of depression, underpinned by aberrant reward processing. As discussed in previous sections, reward-related cognitive impairments have been robustly shown to be driven by abnormally reduced function, activity and/or structure of the dopaminergic circuitry of the brain. Thus, psychotropic agents that increase the bioavailability of dopamine are arguably more precise, hence efficacious, therapeutic tools for addressing symptoms of anhedonia, rather than conventional SSRIs.

1.5.2. Why Dopamine might be the Answer to Treating Anhedonia

Administering the $D_{2/3}$ receptor agonist pramipexole has been shown to yield clinically significant improvements in reward learning amongst depressed individuals (Whitton et al. 2020). This supports the role of dopamine in anhedonia and endorses dopaminergic drugs as potentially useful therapeutic agents for treating MDD due to their greater specificity in addressing deficits in reward processing. Pramipexole has also been tested as a supplementary drug in treatment-resistant depression. In MDD patients who did not experience clinically significant improvements in symptoms, administering pramipexole in addition to concurrent SSRI medication may potentially enhance the latter's efficacy without troublesome side-effects (Cusin et al., 2013; Cassano et al., 2004). This aligns with the supposedly dopaminergic basis of anhedonia and anhedonic MDD patients' unresponsiveness to serotonergic interventions (Dunlop & Nemeroff, 2007). Pramipexole has also been prescribed to individuals diagnosed with Parkinson's Disease (PD) due to the condition's characteristic atrophy of the dopaminergic circuitry to treat symptoms of anhedonia which patients commonly experience. Lemke et al. (2006) observed a significant reduction in depression severity amongst their pramipexole-taking PD patient group compared to clinical control subjects who had not received the drug. Importantly, they reported a decrease in anhedonic symptoms specifically, hence suggesting the dopamine agonist's use for pharmacologically alleviating anhedonia.

1.5.3. Bupropion – Mechanism of Action

This study involves bupropion, a noradrenaline-dopamine reuptake inhibitor (NDRI). Due to its mechanism of action, distinguishing bupropion from more conventional antidepressant drugs such as SSRIs, tricyclic antidepressants (TCA), and monoamine oxidase inhibitors (MAOIs), it is considered an "atypical" medicine for treating MDD. In the UK, bupropion is largely marketed as a pharmacological agent assisting smoking cessation (Fava et al., 2005). Concurrent administration of fluoxetine, an SSRI, has been shown to enhance

bupropion's antidepressant effects by potentiating its action on dopaminergic and noradrenergic receptors, most prominently in the PFC and nucleus accumbens (Li et al., 2002). Conversely, bupropion does not appear to affect serotonergic activity (Ferris et al., 1993). Considering dopamine's role in reward processing, its implications for anhedonia, and the high rate of non-responders amongst SSRI-medicated MDD patients, it appears even more critical to investigate the efficacy and mechanisms of dopaminergic drug treatments (Papakostas, 2006; Zarate et al., 2013).

Bupropion acts by dually inhibiting the reuptake of noradrenaline and dopamine, thereby increasing both neurotransmitters' bioavailability in the synapse (Stahl et al., 2004). For instance, microdialysis in rats revealed time- and dose-dependent increases in dopamine levels upon bupropion administration, particularly in striatal regions such as the nucleus accumbens (Nomikos et al., 1989). A pharmacological agent's affinity denotes the degree to which the drug binds to a particular transporter or receptor at a given concentration of the administered substance (Owens, 1996). Bupropion has shown a greater affinity for noradrenaline than dopamine in that lower doses would be required to achieve a measurable NA-related change in mood versus effects on reward behaviour (Meyer et al., 2002). In contrast, the auto-receptor for dopamine would first need to be de-sensitised, causing a delayed onset for the dopaminergic effects of bupropion.

Considering bupropion's pharmacological profile of dually inhibiting DA and NA, it is worth pointing out that selectively inhibiting the reuptake of noradrenaline can also exert dopaminergic effects in some brain regions. For instance, administering reboxetine, an NRI antidepressant drug, has been found to increase dopamine bioavailability in the prefrontal cortex as well as indirectly modulating dopaminergic firing patterns in the VTA (Linnér et al., 2001). However, despite bupropion being a dual-reuptake inhibitor of both dopamine and noradrenaline, its reward-related effects, suggested by activation of the brain's limbic reward

circuitry, are assumed to be mediated by the drug's dopaminergic properties. This is supported by the low noradrenaline receptor and transporter site density in the striatum (Donnan et al., 1991). Demonstrating neural changes in brain regions high in dopamine receptor density, such as the ventral striatum, after bupropion treatment in depressed individuals would thereby promote dopaminergic antidepressant use as a therapeutic approach for anhedonic MDD.

1.5.4. Neural Explanations for Behavioural Effects

Bearing in mind the differential behavioural functions of dopamine and noradrenaline, Walsh et al. (2017) tested healthy participants on the same instrumental learning task (PILT) that has been used in the present study in addition to measures of emotion processing. Whilst those participants who had received bupropion displayed improvements in mood, their reward processing in terms of performance on the PILT was diminished after bupropion administration. Despite the ethical limitations to directly measuring dopamine levels in humans, microdialysis measurements obtained from animals may offer possible explanations for bupropion's dopaminergic mechanism of action and initial worsening of reward processing (Ito et al., 2000; Weiss et al., 2000).

One account for bupropion's initial impairment of reward processing pertains to its effects on phasic dopamine signalling (Schultz, 2016). Accordingly, the release of dopamine related to reward anticipation has been argued as "time-locked" in that its circulation is tightly controlled and very brief (Stuber et al., 2005; Schultz, 2007). This means that both pre-synaptic release and post-synaptic reuptake of dopamine occur very quickly (Kuhr & Wightman, 1986; Knutson & Gibbs, 2007). Introducing bupropion treatment, however, disrupts the reward circuitry that is assumed to be already dysregulated in anhedonic individuals. As a result, the dopamine release remains the same whilst its re-absorption is inhibited via bupropion, thereby flattening the curve of reward anticipation. This prompts an initial, further impairment in reward processing as a correlate of (temporarily) disrupting the reward circuitry and DA signalling.

Aberrant dopamine signalling has been established as a central mediator of reward prediction error, hence suggesting a possible mechanism of DA drug treatment in MDD (Schultz, 2016).

Importantly, Walsh et al.'s findings, demonstrating an initial deterioration of reward processing, tested the drug in healthy controls whose reward processing was arguably unimpaired to begin with. This is crucial to consider as disrupting a working system would be expected to yield impairments in its function. Conversely, the dopamine system in MDD patients is thought to be impaired as part of their characteristic pathophysiology. Hence, administering bupropion may in fact help shift DA signalling towards healthy patterns and subsequently alleviate symptoms of anhedonia after an *initial* dip in reward learning shortly after drug introduction. The present study aims to examine the effects of bupropion during reward processing in clinically depressed individuals to gain insight into the neural changes that precede behavioural and clinical improvements.

1.5.5. Neural Effects of Bupropion & its Potential for Alleviating Anhedonia

Beyond the discussed behavioural effects of bupropion, findings of its influence on brain activity do hint at encouraging changes in the reward system, a precursor of improved reward learning. Corresponding to the neural dissociation between anticipatory and consummatory responses to reward, Dean et al. (2016) observed enhanced caudal and ventromedial prefrontal activation whilst anticipating a reward amongst individuals who had received bupropion. Consummation of a rewarding outcome showed significantly increased activity in the medial OFC and ventral striatum compared to placebo. Moreover, in healthy participants, relative to the SSRI paroxetine, bupropion was found to better preserve prefrontal and ventral striatal activity (Abler et al., 2011), illustrating its potentially superior use for enhancing neural activity underlying reward processing. However, whilst demonstrating augmented neural activation during reward processing after bupropion treatment is indeed promising, these findings were observed in healthy control subjects. It is therefore necessary to replicate results in clinically

depressed samples to substantiate the evidence in favour of bupropion's potential for treating the neurobiological substrates of anhedonia, including symptomatic improvements. Consequently, the insights of bupropion's neural effect on clinically depressed individuals' reward processing obtained here may contribute to our understanding of the role of dopamine in MDD.

1.6. Study Description

First, this study will establish baseline group differences between unmedicated depressed patients and healthy subjects in the activity of brain regions implicated in reward processing. This will be measured by assessing neural responses during a probabilistic instrumental learning task. Second, MDD patients will receive the NDRI antidepressant drug bupropion for two weeks to study its effects on the neural substrates underlying reward processing compared to unmedicated healthy volunteers. Additionally, self-report measures of anhedonia are taken at baseline and at visit 2 (after bupropion treatment). Anhedonic severity will be correlated with brain activation at both visits, respectively.

1.6.1. Hypotheses

It is expected that unmedicated depressed individuals will display aberrant neural activation at baseline when compared to healthy controls. The administration of bupropion for two weeks in MDD sufferers is anticipated to help normalise their abnormal brain activity during reward processing compared to healthy controls at visit 2. Moreover, it is assumed that symptoms of anhedonia, as indicated by self-report questionnaires, will be elevated amongst patients compared to healthy counterparts at baseline, followed by improvements after bupropion treatment. Lastly, MDD patients' activity of neural structures implicated in reward is expected to be significantly correlated with anhedonic symptom severity.

Chapter 2:

Methodology

2.1. Participant recruitment & screening

Participants were recruited from the general population via opportunity sampling to then undergo initial eligibility screening based on pre-defined inclusion criteria. The screening visit included the Structural Clinical Interview for DSM-IV Axis I psychiatric conditions (SCID-I) and the National Adult Reading Test (NART) to determine estimated verbal IQ, date of birth, BMI, medical history, concomitant medication(s), as well as provision of a urine sample and pregnancy test. The physical examination that all participants underwent included measurements of pulse rate, blood pressure, an electrocardiogram, and blood sample by the study psychiatrist. All participants were either male or female, were required to be between 18 and 50 years of age, have a BMI of 18 to 36 kg/m^2, and be sufficiently fluent in English to understand and complete psychometric testing. Depressed participants included in the study all experienced a current episode of MDD according to the SCID without co-morbid diagnosis of any other Axis I DSM-V psychiatric condition, except for anxiety disorders. Healthy volunteers were included based on no past or current history of any Axis I DSM-IV psychiatric illness. No participants reported recent use of any psychotropic substances within three weeks of test visit 1 or psychological treatment within three months of test visit 1. The study only included subjects whose medical conditions or medications, where present, would not mitigate their own safety or that of the scientific assessment. Any individuals who reported contraindications to MRI scanning (e.g., metal implants), heavy smoking (>10 cigarettes per day), participation in other studies involving the use of medication within three months of this study, or prior experience of the reward task were excluded. Individuals who satisfied all eligibility criteria and remained willing to participate returned between one and four weeks after screening to complete the first test visit. Meanwhile, the information recorded during screening was being processed and the GPs of MDD patients were contacted.

2.2.1. Participant demographics

Participant demographics of healthy and clinically depressed individuals who successfully completed screening and test visit 1, and were considered for the subsequent analysis, are shown below (Tabel 2.1.).

Table 2.1. Breakdown of MDD patients and healthy controls tested on the reward task (PILT), displaying sex, mean age, and mean NART score for each group and overall sample.

	N (Sex)	Age (M ± SD)	NART (M ± SD)
Healthy controls	41 (28F, 13M)	30.20 ± 8.13	116.51 ± 4.82
MDD patients	44 (32F, 12M)	29.68 ± 9.07	115.88 ± 4.30
Total	85 (60F, 25M)	29.93 ± 8.64	116.10 ± 4.57

2.2.2. Questionnaire measures of anhedonic symptom severity

Healthy controls and clinically depressed participants completed the Snaith-Hamilton Pleasure Scale (SHAPS) and the Positive Affect PANAS sub-scale questionnaires to acquire baseline data of anhedonic MDD severity. These data were obtained to allow for a correlation between possible effects of two weeks of bupropion treatment on MDD patients' neural activation during the reward task at test visit 2 and relate those expected neural changes to clinical outcomes. The SHAPS is a 14-item questionnaire which measures severity of anhedonia so that higher scores indicate increased inability to experience pleasure. The Positive Affect PANAS sub-scale (Watson et al., 1988) comprises ten items and assesses individuals whereby lower scores correspond to a reduction in positive affect, suggestive of anhedonia.

2.2.3. Ethical approval

This study received ethical approval by the University of Oxford Clinical Trials and Research Governance Team (CTRG) and NHS Research Ethics Committee (NRES Committee South Central – Berkshire B) (13/SC/0569). It was conducted according to the protocol and provisions of the World Medical Association Declaration of Helsinki. All tested individuals provided their written informed consent for study participation.

2.2.4. Study intervention

Upon enrolment in the study and completion of the fMRI scan at test visit 1, MDD patients received one dose à 150mg of the NDRI-antidepressant drug bupropion daily for 7-10 days. No psychopharmacological treatment was administered to healthy controls as part of this study. After one week, a clinical review visit was implemented to check for side-effects amongst depressed participants. Thereafter, doses were increased to 300mg of bupropion daily to be taken via two tablets à 150mg, ingested in the morning and evening respectively, with at least eight hours in between. If intolerable side-effects occurred, participants were given the choice to either reduce their doses back to 150mg daily or withdraw from the study entirely. Four medicated MDD participants developed intolerable side-effects, all of whom decided to withdraw from further study participation.

2.3. Material

2.3.1. Reward task

The reward task that all participants were tested on was a probabilistic instrumental learning task (PILT), developed by Neurobehavioral Systems Inc. (Berkeley, USA). The task involved monetary wins and losses whose probability of occurrence varied depending on the pairing of

two symbols (Agathodaimon font), as illustrated in Figure 2.1. Each stimulus pairing's probability of entailing a win or loss was based on the likely outcome associated with each individual symbol, respectively. Accordingly, one pair of symbols was associated with a high chance of monetary gain, in that a correct symbol choice would result in winning £1 70% of the time and winning nothing 30% of the time. In high-probability win scenarios, selecting the incorrect symbol would further ensue no win 70% of the time and winning £1 30% of the time. Conversely, the other symbol pairing, being associated with monetary loss, meant that correct symbol choices would entail no loss 70% of the time versus losing £1 in 30% of cases, as well as incorrect choices having a 70% chance of losing £1 alongside losing nothing 30% of the time. The starting sum was £5. Ten familiarisation trials were followed by two experimental runs à 60 trials, each run presenting a different set of four symbols. Each trial involved the random presentation of one of the two symbols that are part of one pairing for 4000ms on a display screen inside the scanner. The symbol was located either to the left or right of a centrally positioned fixation cross which participants were instructed to focus on. Each choice was followed by immediate feedback on the outcome of the preceding choice. For maximal pay-off, participants were asked to learn symbol-outcome associations over the course of the trials, with feedback informing subsequent choices, and allowing them to select high-probability win outcomes whilst avoiding high-probability loss symbols. Outcome measures included the total amount participants won, total wins and losses, choice frequency, percentage consistency (percentage of choices identical to the preceding choice), and reaction time. The PILT's design is illustrated in Figure 2.1.

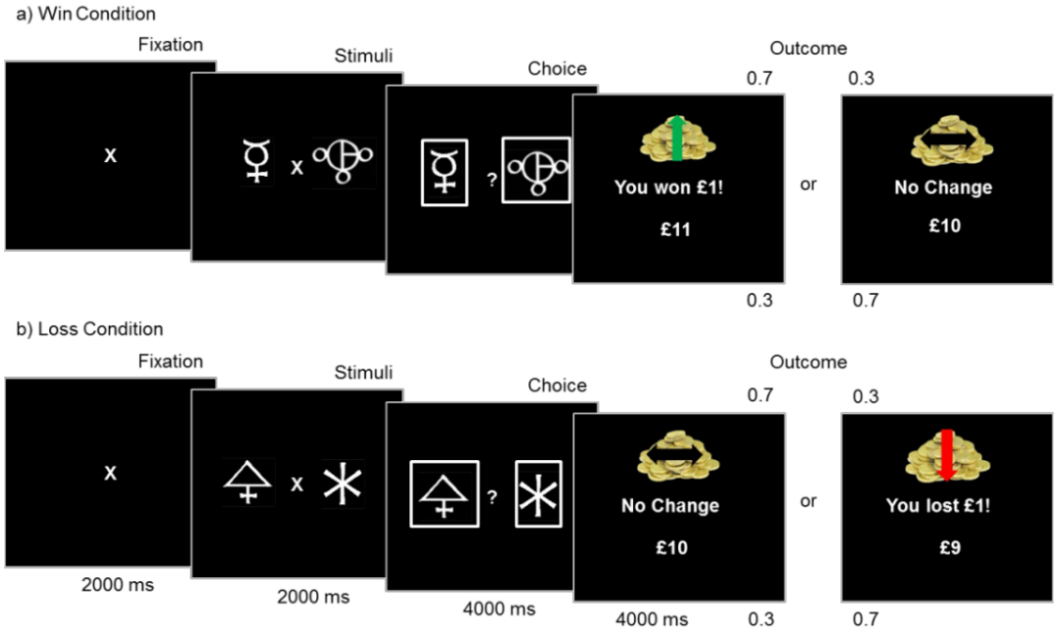

Figure 2.1. Probabilistic Instrumental Learning Task: Test stimuli comprised two pairs of symbols whose outcomes were associated with either a) a win outcome or b) a loss outcome. Individual symbols represented either a 70% (0.7) or 30% (0.3) chance of its associated monetary outcome occurring. Each trial involved the random presentation of one of a given pairing's two symbols, located either to the left or right of a centrally positioned fixation cross which participants were instructed to focus on. Each choice was followed by immediate feedback that participants were instructed to use to maximise monetary pay-offs.

2.4. MRI acquisition

T*1-weighted structural images and T*2-weighted echo planar images (EPIs) depicting blood oxygen level dependent (BOLD) contrast signal were acquired on a 3.0 Tesla TIM Trio scanner. T*1- weighted structural images were acquired using an MPRAGE sequence with the following parameters: voxel resolution 1x1x1mm^3, repetition time (TR) = 2.4s and echo time (TE) = 4.7ms. T*2-weighted EPIs were acquired using the following parameters: voxel resolution of 3x3x3mm^3, TR = 2.71s, TE = 35ms, flip angle of 87^o, slice angle of 300, and whole brain coverage with a total of 45 slices.

2.5. Statistical analysis

MRI data were analysed using FSL (FMRIB Software Library v6.5) tools (https://fsl.fmrib.ox.ac.uk/fsl).

2.5.1. Pre-processing

Pre-processing of the obtained fMRI data involved a number of steps designed to reduce unwanted variability in the data and to improve the validity of statistical analysis. The following steps were therefore implemented for each participant:

Non-brain tissue was removed by means of the FSL tool for brain extraction (BET). Motion correction using FMRIB's Linear Image Registration Tool (MCFLIRT) was implemented to account for head movements inside the scanner, potentially causing movement between volumes. The mean intensity of the dataset changes between subjects and sessions due to extraneous factors (e.g., variability in caffeine levels or heartrate). Thus, to achieve the same mean signal for each subject, grand-mean intensity normalisation of the entire 4D dataset by a single multiplication factor was applied. High-pass temporal filtering was applied to filter out low-frequency drifts related to MRI scanner noise. Spatial smoothing of 5mm served to increase the signal-to-noise ratio. Additionally, functional images were registered to their high-resolution structural scan via the high contrast functional image and BBR using FLIRT (Jenkinson et al., 2002b; Jenkinson & Smith, 2001). Non-linear registration from structural to MNI standard space was then further refined using FNIRT (Anderson et al., 2007a; 2007b), resampling the resolution to 2mm. The data were visually inspected for artefacts, including excessive motion inside the scanner, as well as incorrect registration.

2.5.2. First-level analysis

The first-level analysis examined participants' neural activity at run 1 and run 2 of the PILT individually. Six explanatory variables (EVs) were modelled; win anticipation, loss anticipation, win outcome, loss outcome, no win in win, and no loss in loss. A custom three column format convolved with a gamma haemodynamic response function and its temporal derivatives were used to model the data. Adding temporal derivatives allows the model to fit even when timing is not entirely accurate, for instance, when neural responses occur slightly before or after a pre-specified timing. This serves to compensate for differences between the actual and modelled Haemodynamic Response Function (HRF) as it is fitted on a voxel-by-voxel basis. Adding temporal derivatives is thus able to account for regional differences in HRF, in addition to accounting for differences in slice timing.

Contrasts analysed included means for each condition versus baseline, as well as directional comparisons, as follows. The fifteen contrasts were defined based on the PILT's task-related events:

- Win anticipation versus implicit baseline (fixation cross)
- Loss anticipation versus implicit baseline (fixation cross)
- Win anticipation minus loss anticipation
- Loss anticipation minus win anticipation
- Win outcome versus implicit baseline (fixation cross)
- Loss outcome versus implicit baseline (fixation cross)
- Neutral outcome (neither win nor loss occurs)
- No win in win
- No loss in loss
- Win minus neutral outcome
- Loss minus neutral outcome
- Win minus loss outcome
- Loss minus win outcome
- Win & no loss in loss
- Loss & no win in win

‘Win anticipation minus loss anticipation’, and vice versa, permits the investigation of the most relevant brain regions that are implicated in the anticipation of a win or loss outcome.

Independent samples t-tests were carried out to ascertain no significant differences in absolute and relative motion displacement respectively inside the scanner when comparing depressed and healthy control subjects. This aims to rule out significant group differences in potential motion artefacts as a confounding factor in the subsequent analysis. As significant group differences were found in relative motion, and to further minimise the effects of motion on the data, the motion parameters estimated by MCFLIRT were added to the GLM as confound regressors. Moreover, pulse oximetry and respiratory bellows data collected during the completion of the reward task were used to create 33 physiological noise nuisance regressors, using the PNM (physiological noise model) tool.

2.5.3. Intermediate-level analysis

Since the reward task comprised two runs, an intermediate-level analysis using fixed effects analysis was implemented to estimate each subject’s mean response.

2.5.4. Group-level analysis

Higher-level (group-level) analyses were then carried out using FSL’s tool for non-parametric permutation inference ‘Randomise’ (5000 permutations). In the group-level design, the two explanatory variables (EVs) included “Healthy controls” and “MDD patients”. Contrasts comprised HC>MDD, MDD>HC, HC mean, MDD mean, Mean of HC and MDD combined, and Negative mean.

For the third-level analysis, these data were used to model the between-subject variance and investigate group differences at baseline as well as mean activation for all 15 lower-level contrasts to validate the reward task. To identify significant activation at the whole brain level, statistical images were assessed using a threshold-free cluster enhancement method with family-wise error correction of 0.05 (analogous to a 0.95 threshold within Randomise). Accordingly, the entire brain including all voxels obtained after brain extraction were considered. Many fMRI studies tend to use cluster-based thresholding of statistical images instead, with a height threshold of Z>3.1 to correct for multiple comparisons to decrease the likelihood of Type I statistical errors (false positives). However, this approach has been criticised for its lower statistical robustness (Eklund et al., 2016). Randomise applies different thresholds to the neuroimaging data and automatically selects the threshold that is best suited for the data being analysed. Since Randomise is a non-permutation-based inference tool, it does not rely on the same underlying assumptions that many statistical tests (including FMRIB's FEAT) do, such as the data being normally distributed.

Moreover, Randomise conducted an additional analysis in a mixed repeated measures design, which is required to account for both, baseline measures and data obtained after two weeks of bupropion treatment in MDD patients. Hence, the intermediate-level analysis for participants at visit 1 was ran again, only including those who had also participated in test visit 2. This was done so that the analyses for both visits included the same, hence matched, subjects.

2.5.5. Small Volume Correction & Pre-specified Regions of Interest

In line with Section 1.4. on anatomical structures implicated in reward processing, task-specific regions of interest (ROIs) were generated and examined via Small Volume Correction (SVC). This involved the creation of brain masks to investigate possible significant group differences in neural activation in a more targeted fashion. SVC reduces the number of

multiple comparisons, i.e., decreases the number of voxels that are examined, to increase statistical power whereby differences in pre-specified regions can be better extracted. The pre-specified ROIs thought to be most relevant to reward processing, the PILT test, and the experimental hypotheses to be investigated are:

- Left & right ventral striatum (as defined in the Harvard-Oxford Subcortical Atlas), including nucleus accumbens
- Left & right dorsal striatum (as defined in the Harvard-Oxford Subcortical Atlas), including putamen & caudate nucleus
- Left & right medial and lateral orbitofrontal cortex (created from co-ordinates stated in Kringelbach & Rolls, 2004; left mOFC [x y z = -24 31 -14]; right mOFC [x y z = -24 -31 -14]; left lOFC [x y z = -33 42 -14]; right lOFC [x y z = -33 -42 -14])
- Left & right insular cortex (as defined in the Harvard-Oxford Cortical Atlas)

An additional brain mask was created, including the anatomical regions of interest listed above. These structures comprised the dorsal and ventral striatum, medial and lateral prefrontal cortex, insular cortex, and the anterior cingulate cortex. This ROI brain mask was used to assess the main effect of task across all participants in a more focussed manner to ascertain the task's validity for examining the neural substrates underlying reward processing. All activation clusters are reported using MNI coordinates, and brain regions are described based on the Harvard-Oxford Cortical and Subcortical Structural Atlas, unless otherwise specified.

Chapter 3:

Baseline differences between MDD patients & healthy controls in neural activity during reward processing and symptoms of anhedonia

3.1. Introduction

As outlined in Chapter 1, the research on the neural substrates underlying reward processing strongly suggests this to be modulated by abnormal function of the dopaminergic system, chiefly involving the striatum, orbitofrontal and insular cortices (Schultz, 2016). There is evidence highlighting aberrant reward processing, indicated by impaired reward learning and decreased motivation, as an underpinning mechanism contributing to symptoms of anhedonia in clinical depression (Treadway et al., 2012). The first experimental chapter will therefore examine baseline differences between unmedicated depressed patients and healthy individuals in their neural activation whilst performing an instrumental learning task (PILT; described in Section 2.3.1.). This chapter will also establish the baseline group differences in positive affect and anhedonia between MDD patients and healthy volunteers.

3.2. Objectives

The first experimental chapter's main objectives are as follows:

1) *Main effect of task*: Validating the reward task (PILT) as a tool for assessing different components of reward processing and their underlying neural substrates.
2) *Group differences at baseline*: Establishing group differences in response to task-related events between healthy controls and clinically depressed patients at baseline.
3) *Anhedonic symptom severity & neural activation*: Relating neural activation during reward processing to clinical symptoms of anhedonia in MDD patients.

3.3. Hypotheses

1) *Main effect of task*: Significant mean activation across all participants at the whole-brain level and in pre-specified anatomical regions of interest associated with reward processing, including the VS, medial and lateral OFC, and insular cortex, in response to win versus loss trials.
2) *Group differences at baseline*: Significant group differences between depressed patients and healthy controls in neural activation in response to win versus loss trials at the whole-brain level and for pre-specified anatomical regions of interest.
3) *Relating neural activation during reward processing to clinical symptoms of anhedonia*: Significant positive relationship between aberrant neural activation during reward processing in depressed patients and their symptomatic severity of anhedonia, as measured by the SHAPS and PANAS sub-scale for Positive Affect.

3.4. Results – Questionnaire findings

For participant characterisation of both the depressed and healthy control group in terms of their baseline symptom severity, self-report measures of MDD were taken, displayed in Table 3.1.

Table 3.1. Mean symptom severity, as measured by the HAM-D, SHAPS, and PANAS sub-scale for positive affect self-report questionnaires, for MDD patients and healthy volunteers at baseline.

	HAM-D (M ± SD)	**SHAPS (M ± SD)**	**PA scale (M ± SD)**
Healthy controls	0.85 ± 0.96	19.83 ± 4.23	33.98 ± 6.62
MDD patients	13.18 ± 3.03	34.00 ± 5.34	18.14 ± 5.49

To relate baseline group differences between healthy controls and MDD patients in their neural responses during reward processing to anhedonic symptom severity, a focus was put on the SHAPS questionnaire as well as PANAS sub-scale for Positive Affect. As described in Section 2.2.2., the Snaith-Hamilton Pleasure Scale (SHAPS) assesses severity of anhedonia in terms of higher scores indicating increased impairments in experiencing pleasure. The PANAS sub-scale for Positive Affect monitors individuals' ability to experience positive emotions so that lower scores correspond to diminished positive affect, indicative of anhedonia. Running independent samples t-tests revealed significantly higher mean scores on the SHAPS questionnaire for MDD patients compared to healthy participants at baseline, $t(80.928)=13.450$, $p<0.001$ (Figure 3.1).

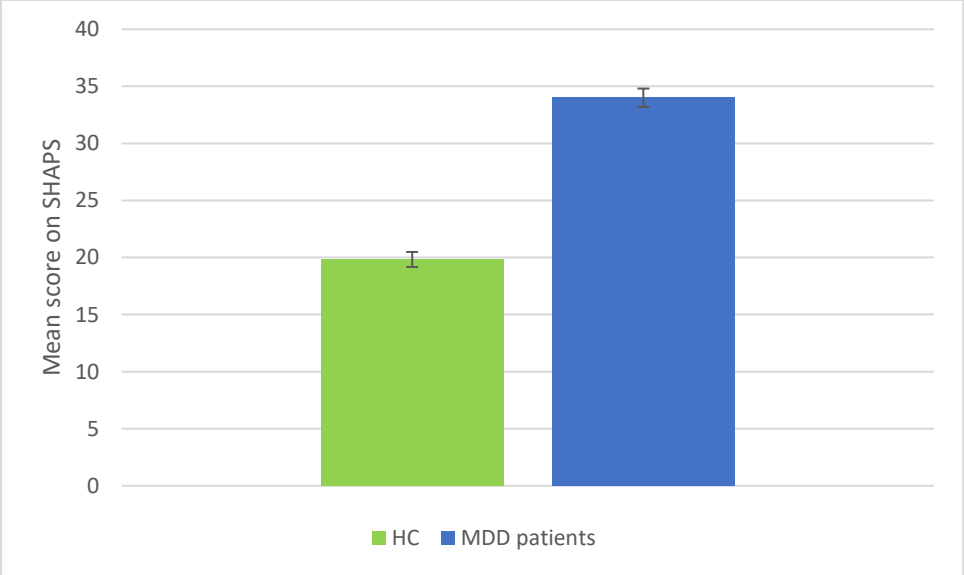

Figure 3.1. Significantly higher mean scores on the Snaith-Hamilton Pleasure Scale (SHAPS) for MDD patients and healthy controls at baseline, $p<0.001$. Error bars display standard error.

Depressed individuals' mean scores on the Positive Affect PANAS sub-scale were found significantly lower than those reported for healthy controls at baseline, $t(77.887)=11.811$, $p<0.001$, illustrated in Figure 3.2.

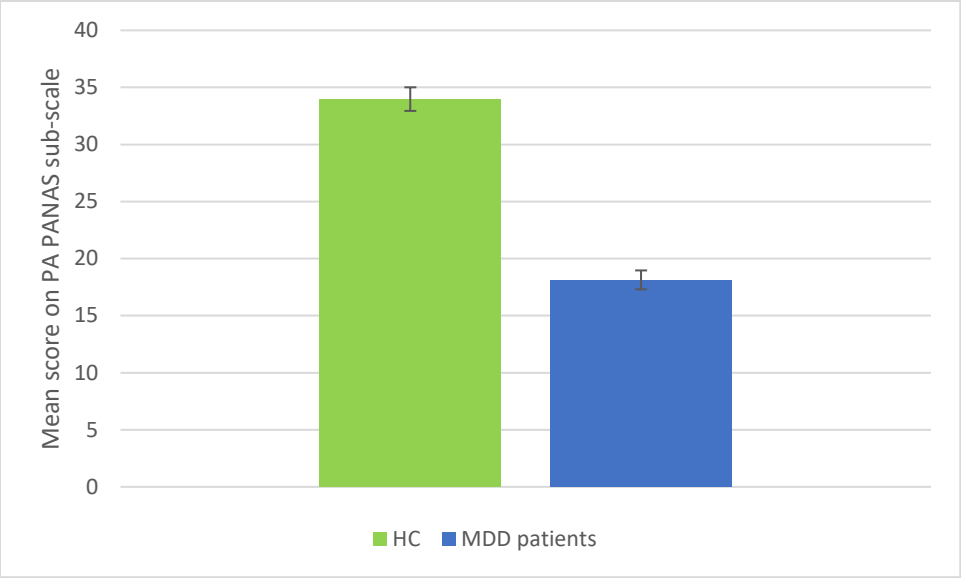

Figure 3.2. Significantly lower mean scores on the Positive Affect Scale for MDD patients and healthy controls at baseline, $p<0.001$. Error bars display standard error.

3.5. Results – Functional MRI findings

3.5.1. Main effect of task

Initially, the validity of the instrumental learning task in assessing the neural substrates underlying its task-related events implicated in reward processing was determined. These activation clusters included the VS (nucleus accumbens), the putamen and caudate nucleus, as well as the lateral and medial orbitofrontal (OFC), and anterior cingulate cortices (ACC), dorsal and ventral divisions. Contrasts between the different task-related events also demonstrated distinct neural activation patterns in response to the anticipation or consummation of win compared to loss outcomes, and vice versa (see Table 3.2.). Please view Appendix A for a complete summary overview of higher-level mean activation clusters across both groups during all 15 task-related events at the whole-brain level at baseline.

Table 3.2. Summary table of higher-level mean neural activation clusters across both groups at the whole-brain level in response to task-related events (lower-level contrasts). Results were corrected for multiple comparisons by TFCE at family-wise error (FWE) rate p=0.05.

Lower-level contrast	Cluster size (voxels)	MNI (x,y,z)	t-score	*p*-value	Structure
Win anticipation – Loss anticipation	14 10	-6 58 12 -36 2 14	4.52 5.20	0.0870* 0.0991*	Frontal pole, paracingulate gyrus Central opercular cortex, extending into insular cortex
Loss anticipation – Win anticipation	2168 1754 1218 208 137 100	-34 -60 40 -20 -2 52 -4 18 44 36 -76 30 -28 -82 26 34 -42 40	5.45 5.57 5.94 3.81 3.58 4.30	0.002 0.003 0.001 0.037 0.043 0.038	Middle frontal gyrus, extending into superior frontal gyrus Precuneus cortex, cuneal cortex Paracingulate gyrus Lateral occipital cortex Supramarginal gyrus Left caudate
Win outcome	58493 113 50 5	-34 -70 -28 8 -76 -38 -16 -56 -36 4 -12 -12	3.00 5.38 3.61 4.11	<0.001 0.026 0.043 0.046	Lateral occipital cortex, extending into inferior temporal gyrus Middle frontal gyrus Superior frontal gyrus, extending into paracingulate gyrus
Loss outcome	34199 7355 2823	-52 -64 -28 52 8 -30 8 42 6	3.40 4.06 5.28	<0.001 <0.001 <0.001	Frontal pole, insular cortex Superior parietal lobule Right thalamus Cingulate gyrus, Left pallidum
No win in win	19554 3649 3091 718 90 44 23 9	34 -34 -26 40 18 -6 -26 -28 32 -52 -46 8 26 -6 32 24 -30 0 -20 -30 -2 6 2 30	3.77 6.94 6.81 6.50 4.12 7.15 6.10 3.91	<0.001 <0.001 <0.001 0.002 0.040 0.015 0.034 0.047	Inferior temporal gyrus Precuneus cortex Left thalamus, left lateral ventricle Right thalamus Parahippocampal gyrus, extending into temporal fusiform cortex Superior temporal gyrus, extending into middle temporal gyrus Orbitofrontal cortex, Frontal pole
No loss in loss	43294	-8 -76 -38	3.12	<0.001	Frontal pole, insular cortex, pallidum, thalamus, hippocampus, putamen (R)
Win – Loss outcome	31453 7348 369 16 6	4 -92 2 -2 32 -18 -20 30 46 -2 -72 44 26 -18 -12	4.48 4.23 5.16 2.67 3.32	<0.001 <0.001 0.015 0.049 0.048	Right accumbens Superior frontal gyrus Inferior temporal gyrus Frontal pole, precentral gyrus, extending into postcentral gyrus Insular cortex, right putamen
Loss – Win outcome	156 104 54	8 14 66 50 -26 -6 -32 20 -10	6.65 8.37 5.95	0.012 0.003 0.033	Frontal operculum cortex, inferior frontal gyrus & OFC Insular cortex
Win & no loss in loss	54088 1967 204 42 6 6	34 -52 -22 -8 64 12 -20 34 46 -26 38 12 -26 -14 -24 -4 -8 28	3.34 5.67 4.56 2.75 2.71 2.44	<0.001 0.005 0.030 0.049 0.049 0.050	Precuneus cortex Right accumbens Frontal pole Superior frontal gyrus Inferior temporal gyrus Right putamen
Loss & no win in win	25	-30 18 -8	7.03	0.025	Insular cortex, orbitofrontal cortex, superior frontal gyrus

*applying a corrected *p*-value yielded no statistically significant mean activation clusters for 'Win anticipation – Loss anticipation'-events; reported MNI coordinates refer to peak voxel locations after applying uncorrected *p*-value

The main effect of task and mean neural activation across all participants in response to task-related events was then further investigated via a more focussed regions of interest analysis. Based on the literature described in Chapter 1, these regions of interest included (orbito)frontal cortical structures, the striatum (dorsal and ventral) divisions, insular, and anterior cingulate cortices. A summary table of the pre-specified anatomical regions of interest implicated in reward processing that were associated with distinct task-related events is shown in Table 3.3.

Table 3.3. Summary table of higher-level mean neural activation clusters across both groups for pre-specified regions of interest in response to task-related events (lower-level contrasts). Results were corrected for multiple comparisons by TFCE at FWE p=0.05.

Lower-level contrast	Cluster size (voxels)	MNI (x,y,z)	t-score	*p*-value	Structure
Win anticipation – Loss anticipation	315	6 48 10	0.96	0.044	Paracingulate cortex, right CC
	42	-28 -30 -14	0.96	0035	Left HPC, left CC/white matter
	33	-36 2 12	0.97	0.035	Central opercular cortex, insula
Loss anticipation – Win anticipation	88	-10 6 4	0.95	0.055	Left cerebral WM, left caudate
	37	20 12 -6	0.92	0.078	Right putamen
	37	-30 24 2	0.97	0.038	Left insular cortex, left CC
Win outcome	4909	28 14 -20	1.0	<0.001	OFC, insular cortex
	1856	6 34 -6	1.0	<0.001	Anterior cingulate gyrus
	441	28 -26 -10	1.0	<0.001	Right hippocampus
	391	-22 -28 -10	1.0	<0.001	Left hippocampus
	328	6 0 30	1.0	0.001	Anterior cingulate gyrus, right C
	16	-18 -6 26	0.95	0.047	Left CC/WM, left caudate
Loss outcome	1596	28 14 -20	1.0	<0.001	OFC, insular cortex
	1334	-42 22 -22	1.0	<0.001	Temporal pole, OFC, left CC
	838	10 42 6	1.0	<0.001	Anterior cingulate gyrus (right)
	812	10 8 -2	1.0	<0.001	Right caudate, right accumbens
	122	22 -28 -4	1.0	<0.001	Right thalamus, right WM
	60	-20 -30 -2	1.0	0.001	Left thalamus, left cerebral WM
No win in win	890	30 18 -12	1.0	<0.001	Insular cortex, OFC, right CC
	271	-26 26 -6	1.0	0.002	OFC, left CC/white matter (WM)
	54	24 -30 0	1.0	0.003	Right cerebral WM, thalamus
	22	-20 -30 -2	0.97	0.027	Left thalamus, left cerebral WM
No loss in loss	512	40 18 -6	1.0	<0.001	Insular cortex, OFC, right CC
	215	-36 18 -6	1.0	0.006	Insular cortex, OFC, left CC
	131	24 -30 -4	0.99	<0.001	Right cerebral white matter
	74	-20 -30 0	1.0	<0.001	Left thalamus, left cerebral WM
	52	-16 -4 26	1.0	0.003	Left cerebral WM, left caudate
Win – Loss outcome	1803	-4 32 -16	1.0	<0.001	Medial frontal cortex
	729	16 6 -16	1.0	<0.001	OFC, right cerebral cortex
	663	-10 4 -14	1.0	<0.001	Left CC, left accumbens
	109	-24 -34 -2	0.97	0.033	Left thalamus, hippocampus
	99	26 -32 -4	0.97	0.030	Right HPC, cerebral WM

Loss – Win outcome	654 553	-30 20 -10 42 24 -2	1.0 1.0	0.001 0.005	OFC, insular cortex, left CC Frontal operculum, OFC
Win & no loss in loss	926 632 586 275 210 55 31	-10 4 -14 16 6 -14 -14 -34 6 26 -36 -4 30 -12 0 -16 -6 26 20 -4 24	1.0 1.0 0.99 0.97 0.99 0.95 0.98	<0.001 <0.001 0.011 0.031 0.015 0.048 0.022	Left cerebral cortex, accumbens OFC, right CC/WM, putamen Left thalamus, left cerebral WM Right HPC, right cerebral WM Right putamen Left lateral ventricle, caudate Right cerebral WM, caudate
Loss & no win in win	412 391	-30 18 -8 50 20 -2	1.0 0.98	<0.001 0.019	Insular cortex, OFC, left CC Inferior frontal gyrus, OFC

As shown in Table 3.3., examining mean activation across all study participants for pre-specified ROIs yielded significant brain activity in the neural substrates implicated in reward processing in response to win versus loss trials and those denoted by RPE. Please view Appendix B for a complete summary overview of higher-level mean activation clusters across both groups during all 15 task-related events for pre-specified regions of interest at baseline. Studying the main effect of task on anatomical ROIs also revealed differential neural activation patterns associated with the consummation compared to anticipation of a win versus loss outcome. Namely, computing (the difference between) a win or loss outcome, i.e., consummation, most prominently involved orbitofrontal activation with some striatal responses, albeit to a lesser extent. Similarly, trials denoted by reward prediction error, such as 'No win in win' and 'No loss in loss', also appeared to be more strongly associated with OFC in addition to insular activation. In contrast, anticipation of win or loss outcomes has been found to be partly underpinned by striatal activation, as shown for 'Loss anticipation – Win anticipation'-scenarios eliciting right putamen activation. The neural main effect of task across all participants during each of the 15 task-related events is illustrated in Figure 3.3.

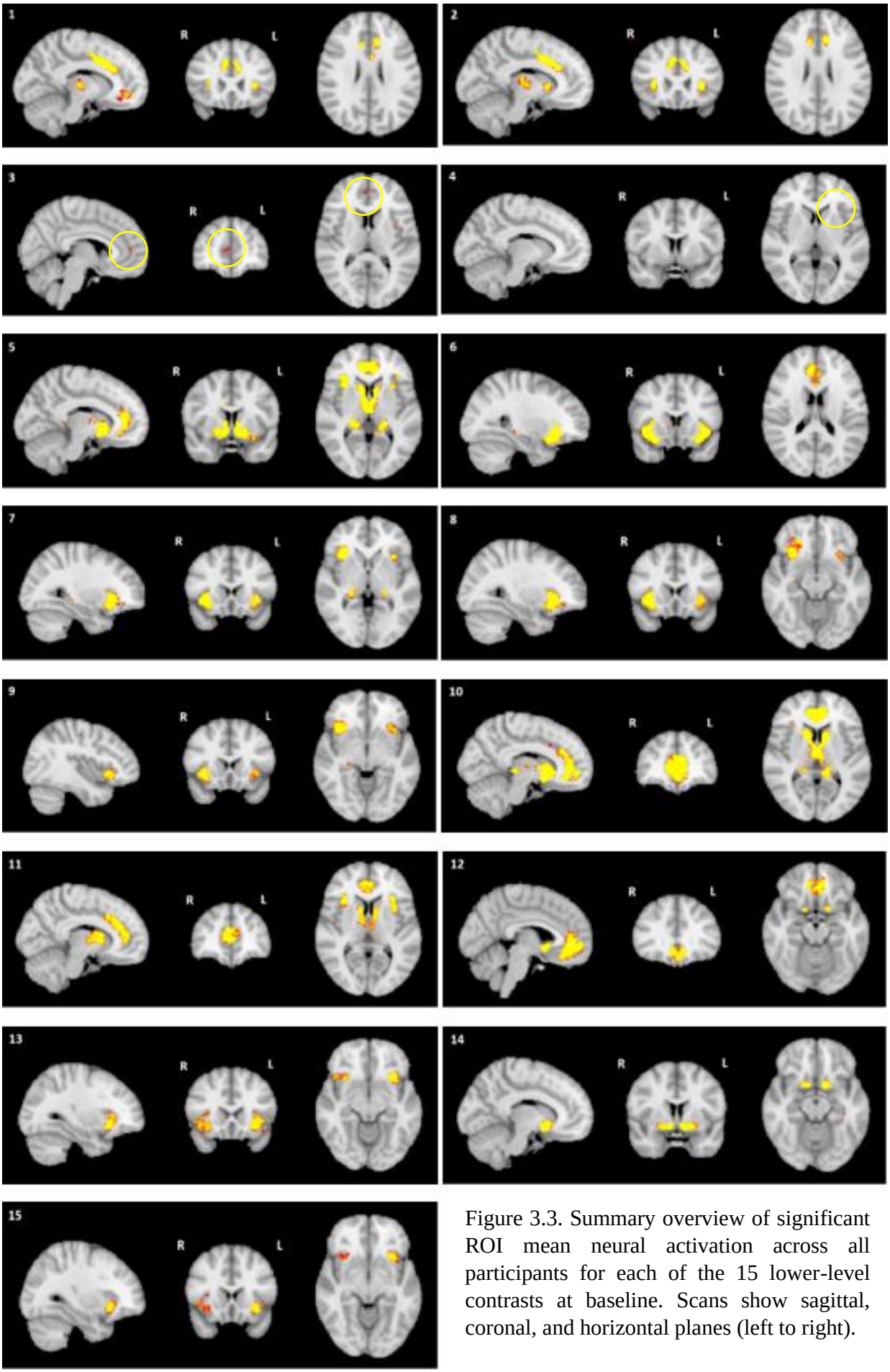

Figure 3.3. Summary overview of significant ROI mean neural activation across all participants for each of the 15 lower-level contrasts at baseline. Scans show sagittal, coronal, and horizontal planes (left to right).

3.5.2. Group differences between depressed individuals & healthy controls at baseline

3.5.2.1. Whole-brain analysis

Comparison of HC and MDD participants at the whole brain level at baseline did not reveal any significant group differences in neural activity in response to the consummation of a win or loss outcome (versus fixation cross), nor did the anticipation of either a win or loss outcome. However, computing the difference between the consummation of a win or loss outcome did show statistically significant group differences. Accordingly, neural activity amongst MDD patients in response to 'Win minus loss outcome' was significantly lower than that measured in healthy controls in three separate clusters in the bilateral occipital cortex. Conversely, depressed participants displayed significantly greater neural activation for 'Loss minus win outcome' than did control subjects in four separate clusters in the bilateral occipital cortex. Accounting for brain activity in response to 'Neutral outcomes' did not affect group differences in neural activation. When exposed to 'Win & no loss in loss' scenarios (positive outcome), MDD patients' brain activity was significantly reduced compared to healthy volunteers in the right inferior frontal gyrus whereas depressed participants' responses to 'Loss & no win in win'-scenarios (negative outcome) were found significantly greater than their healthy counterparts. The neural activation clusters of these group differences at the whole brain level at baseline are summarised in Table 3.4. below.

Table 3.4. Overview of significant group differences between depressed individuals and healthy participants at the whole brain level at baseline. Results were corrected for multiple comparisons by TFCE at FWE p=0.05.

Lower-level contrasts	Direction of group comparison	Cluster size (voxels)	MNI (x,y,z)	t-score	*p*-value	Structure
Win – Loss outcome	HC > MDD	862	24 -86 26	4.22	0.0300	Occipital cortex
		454	14 -78 -12	4.36	0.0350	Lingual gyrus; right CC
		274	-32 -84 16	4.67	0.0270	Occipital cortex; left CC
Win & no loss in loss	HC > MDD	62	48 32 6	5.39	0.0300	R inferior frontal gyrus
		30	12 56 32	4.77	0.0410	Frontal pole; right CC
Loss & no win in win	MDD > HC	44	48 32 6	5.39	0.0340	R inferior frontal gyrus
		20	12 56 32	4.77	0.0440	Frontal pole; right CC

As noted in Table 3.4., the significant group differences between healthy controls and depressed patients in baseline neural activation at the whole brain level was largely seen in visual brain regions, such as the occipital cortex and lingual gyrus. Additionally, brain activity in the frontal pole was found significantly greater for healthy compared to MDD participants during 'Win & no loss in loss'-scenarios, and significantly higher for patients in response to 'Loss & no win in win'-events, respectively. The results of the whole brain analysis on significant group differences were further investigated by means of a regions of interest (ROI) analysis, examining neural activity in relevant anatomical structures more specifically.

3.5.2.2. Analysis of pre-specified anatomical regions of interest

Corresponding to the literature on neural structures implicated in different components of reward processing, anatomical regions of interest (ROIs) were defined, and brain masks created (see *2.4.5.*). Investigating possible group differences via ROI analysis increases the specificity and power of the statistical analyses as fewer voxels are examined. As described in *2.4.5.*, extracted ROIs are as follows:

- Left & right ventral striatum (nucleus accumbens)
- Left & right dorsal striatum (caudate & putamen)
- Left & right medial and lateral orbitofrontal cortex
- Left & right insular cortex

Inspecting neural activation in brain regions implicated in reward processing yielded a number of statistically significant group differences between HC and MDD participants, as shown in Table 3.5.

Table 3.5. Overview of statistically significant group differences between healthy controls and depressed patients for pre-specified anatomical regions of interest at task-related events (lower-level contrasts) at baseline. Results were corrected for multiple comparisons by TFCE at FWE p=0.05.

Anatomical ROI	Lower-level contrast	Direction of group comparison	Cluster size (voxels)	MNI (x,y,z)	t-score	*p*-value
Putamen (L)	Neutral outcome	MDD > HC	44	-24 4 8	3.18	0.0294
Putamen (L)	No win in win	MDD > HC	241	-28 8 4	3.39	0.0080
Putamen (L)	Win – Neutral	HC > MDD	28 13	-24 2 10 -32 -10 -2	3.12 2.92	0.0390 0.0450
Putamen (L)	Win & no loss in loss	HC > MDD	46	-24 -6 10	3.92	0.0152
Putamen (L)	Loss & no win in win	MDD > HC	36	-24 -6 10	3.92	0.0172
Putamen (R)	No win in win	MDD > HC	212	28 2 -2	3.30	0.0112
Putamen (R)	Win – Neutral	HC > MDD	152	28 0 2	3.86	0.0074
Putamen (R)	Win & no loss in loss	HC > MDD	216	30 2 4	3.35	0.0112
Putamen (R)	Loss & no win in win	MDD > HC	196	30 2 4	3.35	0.0112
Caudate (L)	No win in win	MDD > HC	9	-10 8 12	2.74	0.0472
Caudate (R)	Win & no loss in loss	HC > MDD	20 15	18 2 20 14 18 10	3.41 2.75	0.0310 0.0400
Caudate (R)	Loss & no win in win	MDD > HC	11 10	18 2 20 14 18 10	3.41 2.75	0.0330 0.0440
Accumbens (R)	Win & no loss in loss	HC > MDD	9	8 6 -8	2.80	0.0326
Accumbens (R)	Loss & no win in win	MDD > HC	7	8 6 -8	2.80	0.0344
Insula (L)	No win in win	MDD > HC	33	-34 8 4	3.10	0.0288
Lateral OFC (L)	Win & no loss in loss	HC > MDD	2	-36 34 -10	3.57	0.0430
Lateral OFC (L)	Loss & no win in win	MDD > HC	2	-36 34 -10	3.57	0.0426
Lateral OFC (R)	Loss – Neutral	MDD > HC	57	36 40 -6	2.55	0.0183
PILT ROI mask	Win & no loss in loss	HC > MDD	17	30 2 2	3.32	0.0474

According to Table 3.5., the significant group differences in local neural activation obtained at baseline largely included task-related events that denoted a reward prediction error (RPE; see Chapter 1). Corresponding contrasts such as ‘No win in win’, ‘Win & no loss in loss’, and ‘Loss & no win in win’ were plotted to illustrate the direction of group comparison. Resulting figures are presented and described in the following sections of this chapter.

3.5.2.2.1.1. ‘No win in win’ – Bilateral dorsal striatum

The ROI analysis at baseline revealed significant group differences between depressed and healthy participants in activation of numerous reward-related brain regions in response to ‘No win in win’-scenarios. Examining neural activity during negative prediction error has hence consistently showed greater neural activity amongst patients versus healthy controls. Accordingly, MDD patients displayed a lower reduction during ‘No win in win’-scenarios in the bilateral putamen compared to healthy subjects, illustrated in Figures 3.4. and 3.5. below.

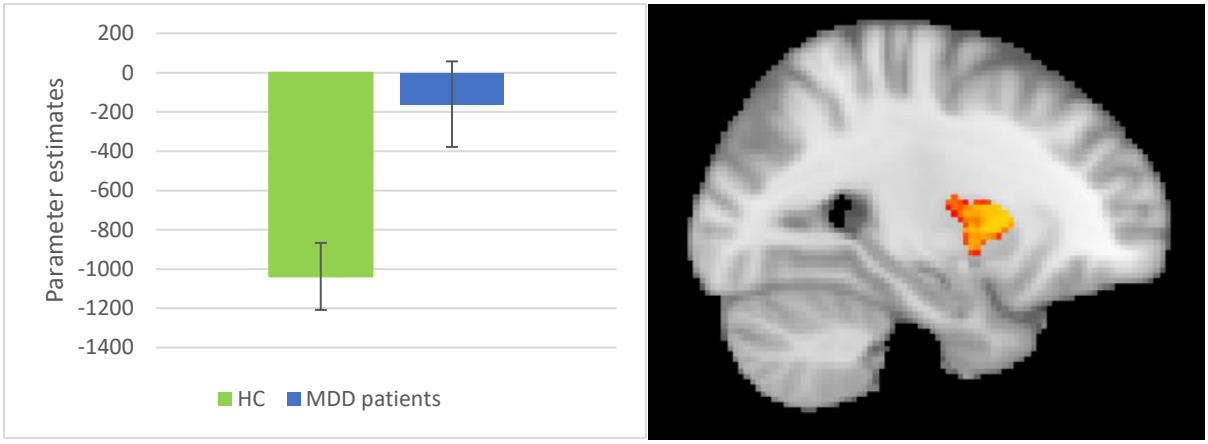

Figure 3.4. Significantly lower reduction in left putamen activity in response to ‘No win in win’-scenarios in depressed participants compared to healthy controls at baseline. Error bars display standard error (SE; left). Neural activation of the left putamen (x y z = -28 8 4) for ‘No win in win’ (right).

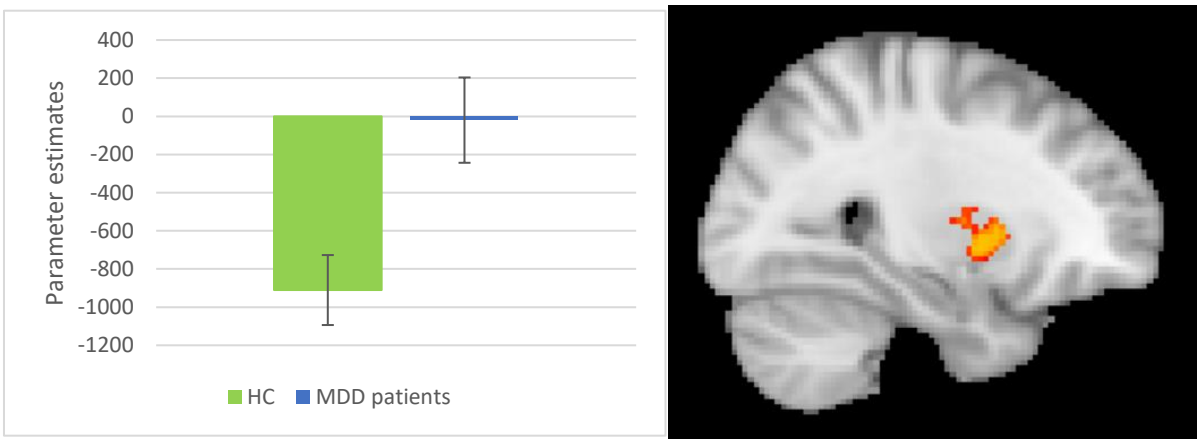

Figure 3.5. Significantly lower reduction in right putamen activity in response to ‘No win in win’-scenarios in MDD patients compared to HC at baseline. Error bars display SE (left). Neural activation pattern of right putamen (x y z = 28 2 -2) for ‘No win in win’ (right).

Moreover, baseline activity in the left caudate indicated significant greater activity during 'No win in win'-scenarios amongst MDD patients whereas healthy volunteers' responses were significantly reduced, shown in Figure 3.6. below.

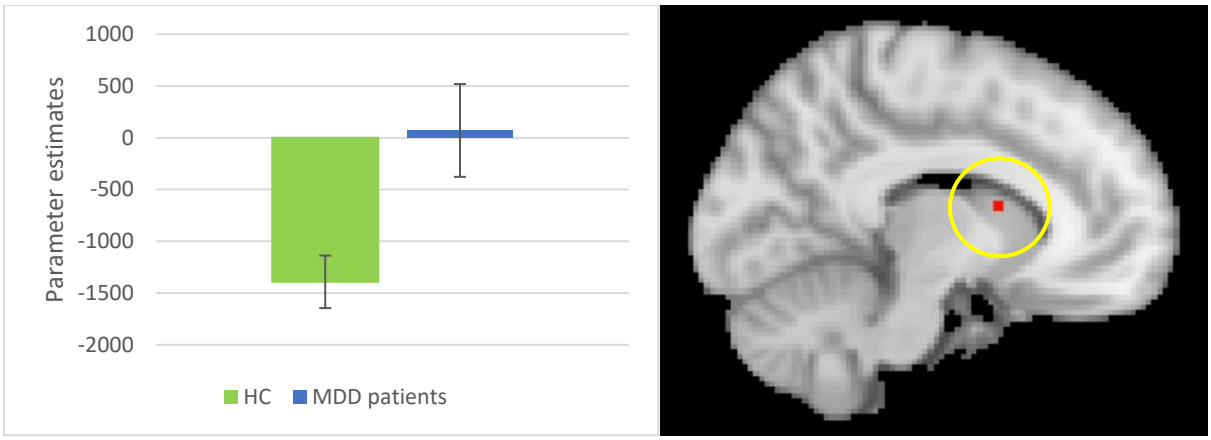

Figure 3.6. Significantly greater left caudate activity in response to 'No win in win'-scenarios in depressed participants compared to healthy controls at baseline. Error bars display SE (left). Neural activation pattern of left caudate (x y z = -10 8 12) for 'No win in win' at baseline (right).

3.5.2.2.1.2. 'No win in win' – Left insular cortex

Activation of the left insular cortex aligned with the neural patterns observed in bilateral dorsal striatal activity during 'No win in win'-events in that MDD patients demonstrated significantly less reduction in left insular activity than did healthy controls (see Figure 3.7.).

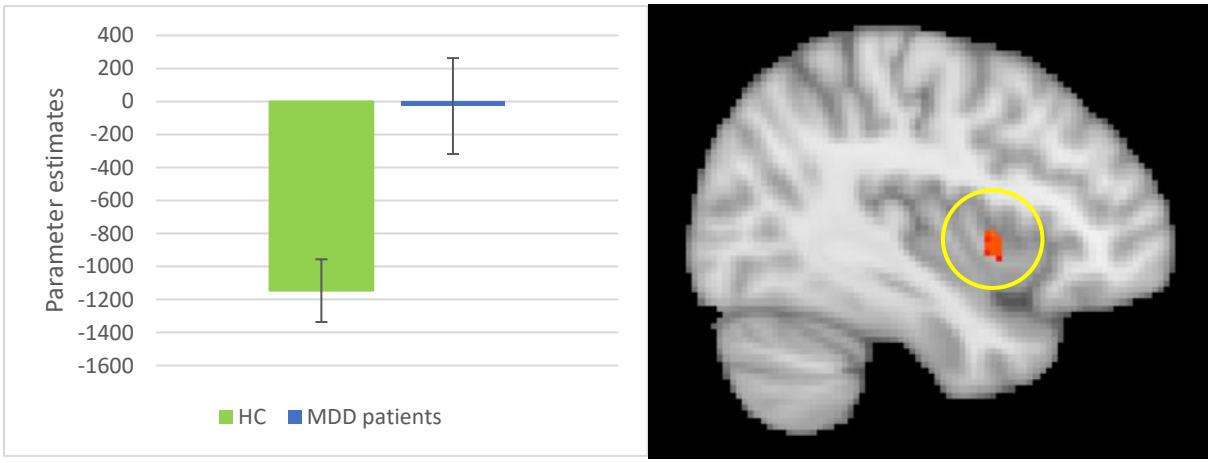

Figure 3.7. Significantly lower reduction in left insular activity in response to 'No win in win'-scenarios in MDD patients compared to healthy controls at baseline. Error bars display SE (left). Neural activation pattern of left insular cortex (x y z = -34 8 4) for 'No win in win' (right).

3.5.2.2.2.1. ‘Win & no loss in loss’ – Bilateral dorsal striatum

Examining dorsal striatal activation during ‘Win & no loss in loss’-scenarios at baseline revealed significantly increased bilateral putamen activity in healthy participants compared to depressed individuals, who displayed a marked reduction in left and right putamen activity. These findings are illustrated in Figures 3.8. and 3.9. below.

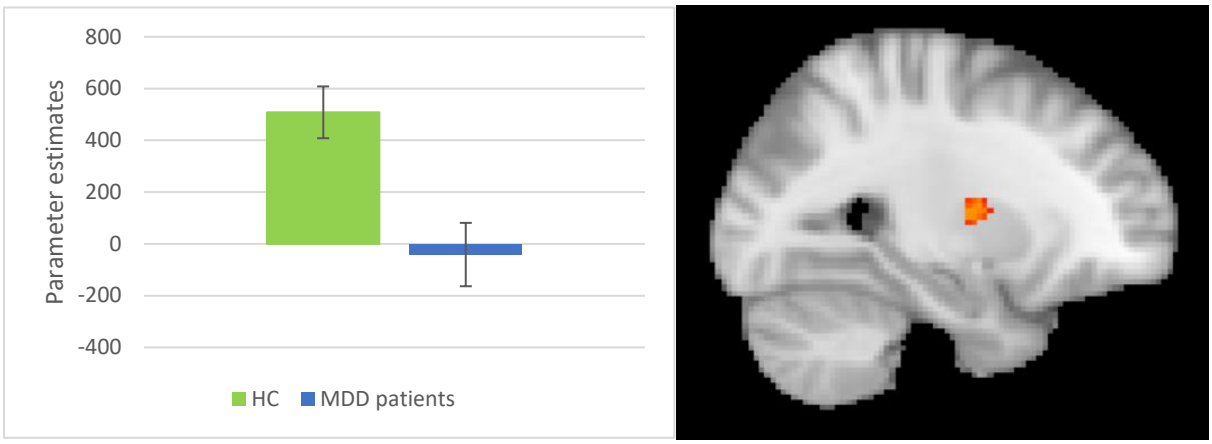

Figure 3.8. Significantly greater left putamen activity in response to ‘Win & no loss in loss’-scenarios in healthy controls compared to MDD patients at baseline. Error bars display SE (left). Neural activation of the left putamen (x y z = -24 -6 10) for ‘Win & no loss in loss’ (right).

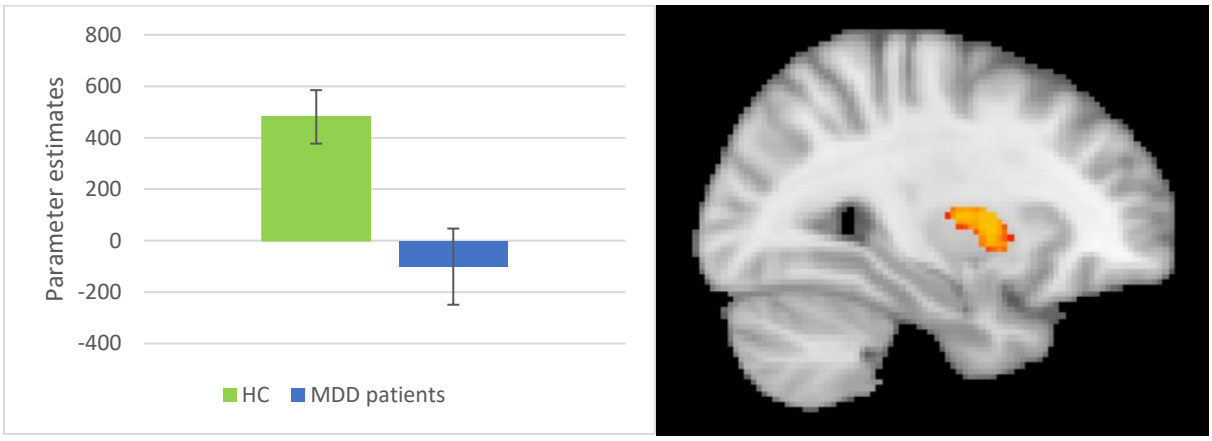

Figure 3.9. Significantly greater right putamen activity in response to ‘Win & no loss in loss’-scenarios in healthy controls compared to MDD patients at baseline. Error bars display SE (left). Neural activation of the right putamen (x y z = 30 2 4) for ‘Win & no loss in loss’ (right).

Furthermore, baseline right caudate activity in response to 'Win & no loss in loss'-events was found to be significantly increased amongst healthy controls. Depressed patients, however, showed a significant reduction in right caudate activation, as displayed in Figure 3.10.

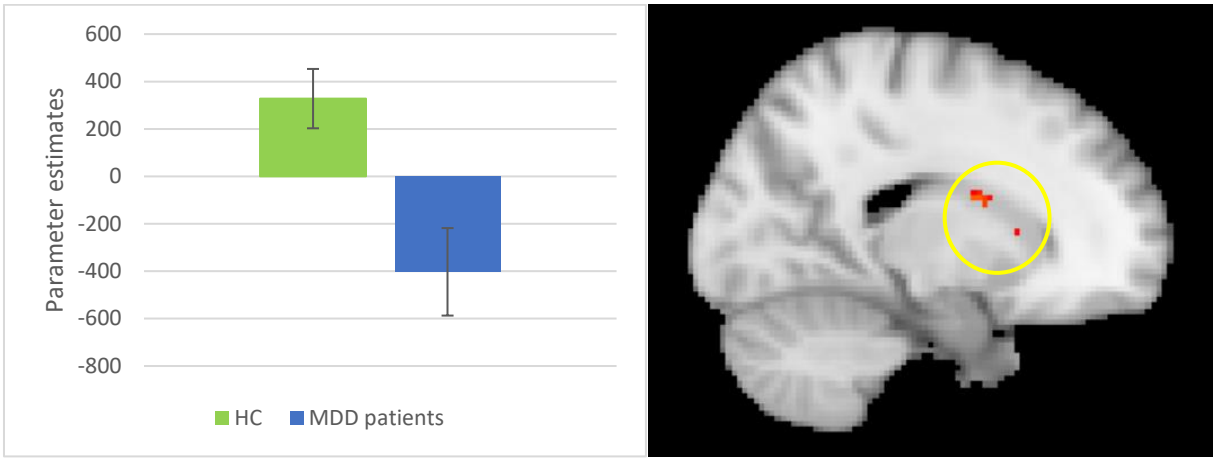

Figure 3.10. Significantly greater right caudate activity in response to 'Win & no loss in loss'-scenarios in healthy controls compared to MDD patients at baseline. Error bars display SE (left). Neural activation of the right caudate (x y z = 18 2 20) for 'Win & no loss in loss' (right).

3.5.2.2.2.2. 'Win & no loss in loss' – Right ventral striatum

Exposing participants to 'Win & no loss in loss'-scenarios also revealed some baseline group differences between HC and MDD participants in ventral striatal activation. Accordingly, healthy controls demonstrated a significantly greater increase in right nucleus accumbens activity than that observed in clinically depressed participants. Parameter estimates for both groups and the neural activation of the right ventral striatum during 'Win & no loss in loss'-events at baseline are hence presented in Figure 3.11.

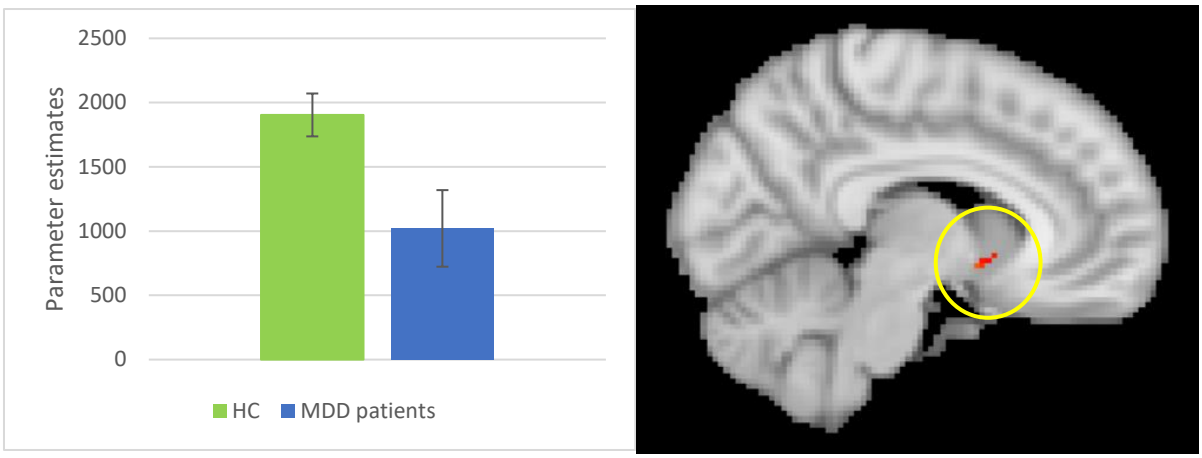

Figure 3.11. Significantly greater right accumbens activity in response to 'Win & no loss in loss'-scenarios in HC compared to MDD patients at baseline. Error bars display SE (left). Neural activation of the right accumbens (x y z = 8 6 -8) for 'Win & no loss in loss' (right).

3.5.2.2.3.1. 'Loss & no win in win' – Bilateral dorsal striatum

Investigating baseline neural activation in response negative RPE and negative outcome, as operationalised by 'Loss & no win in win'-events yielded further significant group differences. Analogous to findings for 'No win in win'-scenarios, 'Loss & no win in win'-events were marked by significantly greater increase in dorsal striatal activity, or lower reduction thereof, in MDD patients compared to healthy volunteers. Accordingly, depressed individuals displayed significantly larger increases in bilateral putamen response whilst healthy controls were characterised by a significant decrease in bilateral putamen activation during 'Loss & no win in win'. These results are illustrated in Figures 3.12. and 3.13.

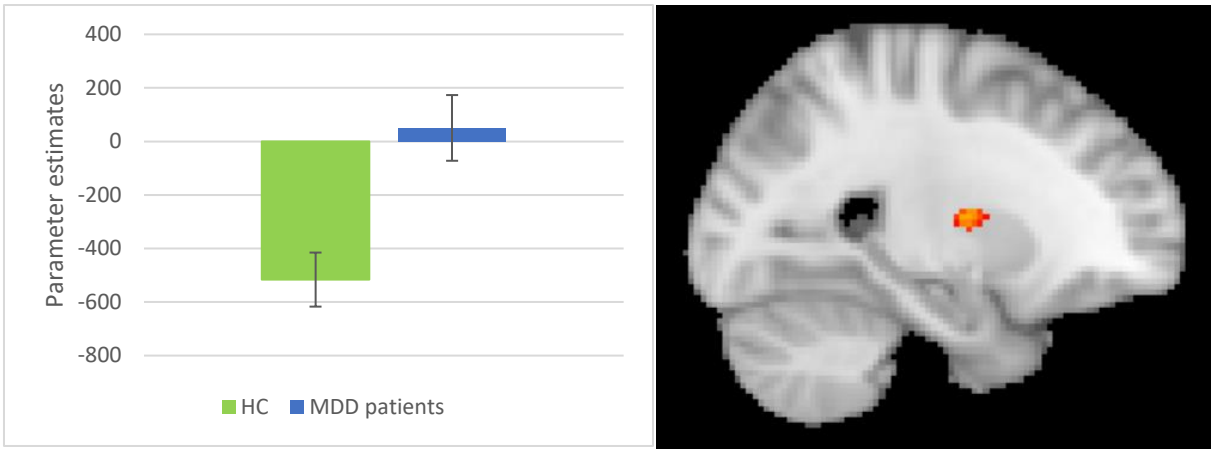

Figure 3.12. Significantly greater left putamen activity in response to 'Loss & no win in win'-scenarios in MDD patients compared to healthy controls at baseline. Error bars display SE (left). Neural activation of the left putamen (x y z = -24 -6 10) for 'Loss & no win in win' (right).

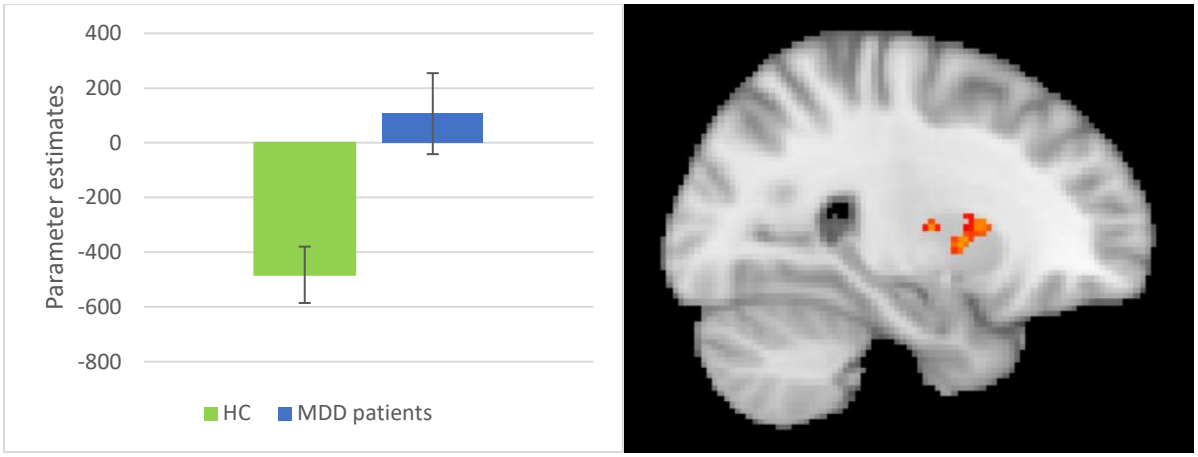

Figure 3.13. Significantly greater right putamen activity in response to 'Loss & no win in win'-scenarios in MDD patients compared to healthy controls at baseline. Error bars display SE (left). Neural activation of the right putamen (x y z = 30 2 4) for 'Loss & no win in win' (right).

Significantly greater increase in brain activation during 'Loss & no win in win'-events at baseline amongst MDD patients in addition to a larger reduction in neural response in the control group was also obtained for right caudate activity, presented in Figure 3.14.

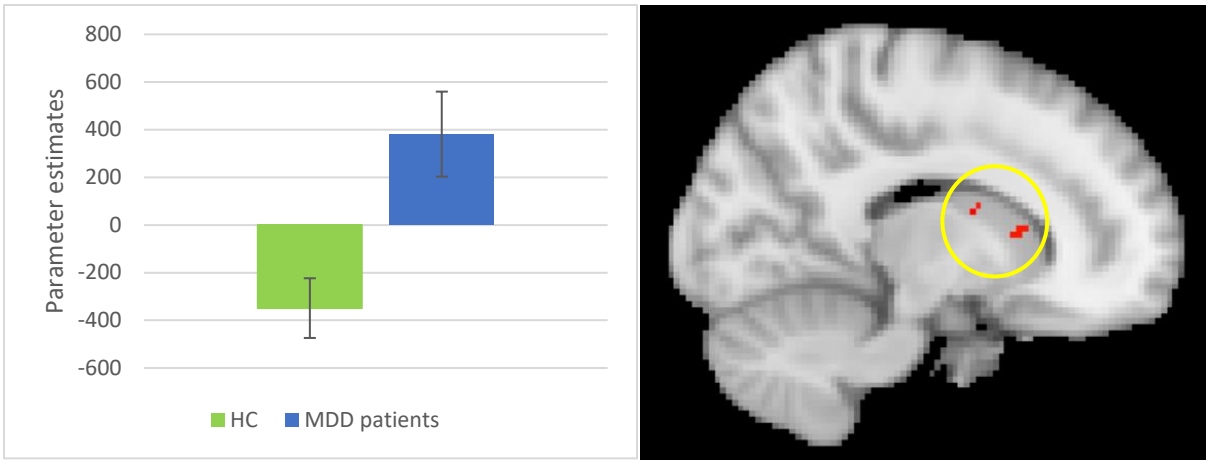

Figure 3.14. Significantly greater right caudate activity in response to 'Loss & no win in win'-scenarios in MDD patients compared to healthy controls at baseline. Error bars display SE (left). Neural activation of the right caudate (x y z = 18 2 20) for 'Loss & no win in win'-events (right).

3.5.2.2.3.2. 'Loss & no win in win' – Right ventral striatum

Right ventral striatal activity during 'Loss & no win in win'-scenarios at baseline was found to differ between both groups in that clinically depressed participants' right accumbens activity was significantly less decreased than neural activation amongst controls. Please see Figure 3.15. below for parameter estimates obtained from both groups and accumbens activity during 'Loss & no win in win'.

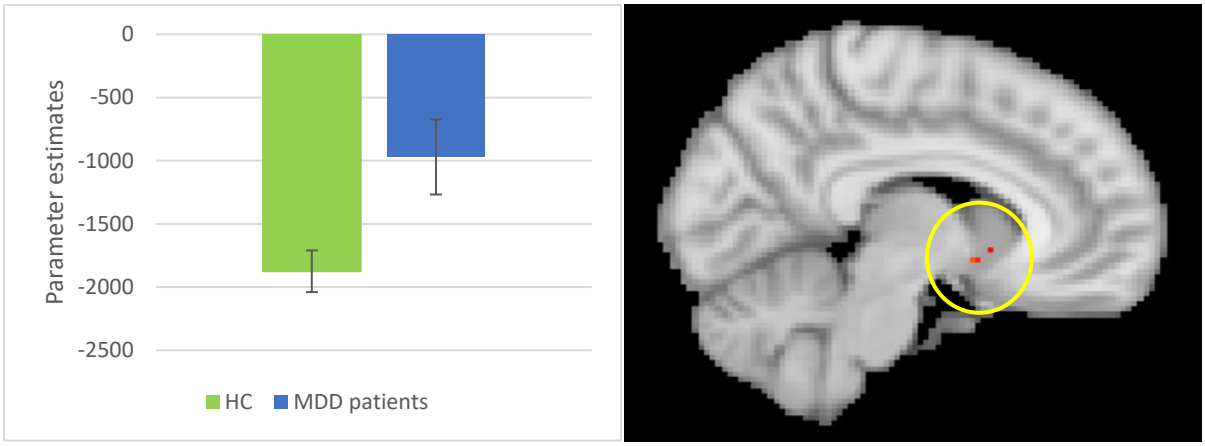

Figure 3.15. Significantly lower reduction in right accumbens activity in response to 'Loss & no win in win'-scenarios in MDD patients compared to HC at baseline. Error bars display SE (left). Neural activation of the right accumbens (x y z = 8 6 -8) for 'Loss & no win in win' (right).

Pearson's correlation between MDD patients' parameter estimates and their scores on the SHAPS and Positive Affect PANAS sub-scale questionnaires, respectively, were calculated for all lower-level contrasts at baseline. Doing so did not reveal any significant relationships between anhedonic symptom severity and neural activity during reward processing on the PILT (SHAPS: $-0.03 \leq$ Pearson's $r \leq 0.28$, $p \geq 0.062$; PANAS: $-0.13 \leq$ Pearson's $r \leq 0.09$, $p \geq 0.420$).

3.6. Summary of findings

This first experimental chapter aimed to validate the probabilistic instrumental learning task (PILT) for assessing neural activation patterns implicated in reward processing in response to specific task-related events. Studying the mean activation across all participants, at the whole brain level and with a focussed ROI approach, confirmed a significant main effect of task that aligns with the literature on neural substrates underlying positive and negative reward. This chapter also sought to establish significant group differences between unmedicated depressed patients and healthy volunteers in neural activation during task-related events at baseline.

Analyses at the whole brain level revealed significantly greater neural responses amongst MDD patients compared to healthy controls during negative reward scenarios, including 'Loss minus win outcome' and 'Loss & no win in win'-scenarios. Conversely, depressed individuals showed significantly reduced brain activity when computing positive reward scenarios compared to healthy participants, indicated by 'Win minus loss outcome' and 'Win & no loss in loss'-events. These group differences in neural activation predominantly pertained to brain regions involved in visual processing, namely the occipital cortex and lingual gyrus.

The trend of greater neural activation amongst MDD patients in response to negative reward/loss scenarios and decreased activity during positive reward scenarios, respectively, was also reflected in the results of subsequent ROI analyses. Clinically depressed individuals were characterised by showing greater brain activation when processing 'No win in win' as well as

‘Loss & no win in win’-scenarios. This was evidenced by responses in the bilateral dorsal striatum, the right ventral striatum (accumbens), and insular cortex. The MDD group’s activation in these anatomical regions implicated in reward during ‘Win & no loss in loss’, however, was found to be significantly lower than that observed in healthy controls. Moreover, ‘Win minus neutral outcome’ and ‘Loss minus neutral outcome’ elicited greater neural responses amongst healthy and depressed participants, respectively. The group differences in activational effects on left orbitofrontal activity were marginal and will therefore not be further interpreted in the upcoming discussion.

Anhedonic symptom severity at baseline was significantly greater amongst clinically depressed participants compared to healthy controls, indicated by mean scores on the SHAPS and Positive Affect PANAS sub-scale questionnaires. Baseline group differences in anhedonia and brain activity during reward processing were not found to be significantly correlated.

3.7. Discussion

The first experimental chapter sought to replicate that the reward task used here activated reward-relevant neural circuitry. Thereafter, baseline group differences between unmedicated MDD patients and healthy individuals in their brain activation during different task-related events were established. First, the probabilistic instrumental learning task (PILT) was successfully validated as an appropriate tool for assessing the neural mechanisms underpinning reward learning. This was evidenced by significant mean activation of anatomical regions of interest that have been robustly associated with reward and punishment, namely key nodes within the mesocorticolimbic pathway (Knutson et al., 2001; Lui et al., 2011). Moreover, research has shown dissociable neural activity underpinning the computation of anticipating versus experiencing a rewarding outcome, or the absence thereof, in addition to appraisal of aversive information (Schultz et al., 1997; Tobler et al., 2003). Present findings corroborated

this, by yielding differential brain activation clusters associated with task-related events denoting win versus loss outcomes, anticipating such scenarios, as well as the disparity between either, i.e., reward prediction error (RPE; Abler et al., 2006). Specifically, the consummation of a win or loss outcome was found to be most strongly underpinned by orbitofrontal activation. Meanwhile, striatal responses played a more prominent role during anticipation trials, however, mostly featuring dorsal instead of ventral divisions, hence partially aligning with the empirical data (Knutson et al., 2001). It also substantiates prior observations that insular activation was a major neural marker of computing RPE (Billeke et al., 2020). These results collectively support the dissociation of different components of processing reward-related information.

Second, significant group differences in neural activation during reward processing were found between MDD patients and healthy volunteers at the whole-brain level and for pre-specified anatomical regions of interest. At the whole-brain level, depressed participants' brain activity was significantly increased for negative outcomes paired with negative RPE compared to HC subjects whereas positive outcomes combined with positive RPE yielded a decrease in patients' activity. Albeit aligning with research suggesting differential sensitivity to positive versus negative reward in depression (Bress et al., 2013; Must et al., 2006), the WBA group differences obtained here primarily involved brain regions responsible for visual processing, not reward-related structures per se, in contrast to what would be expected. Importantly, there is some evidence for aberrant visual processing in MDD, including implications for processing speed of cues that may have affected group differences during reward stimulus processing, too. Additionally, WBA group differences in activation of the visual system coincided with some frontal cortical activation, alluding to research on attentional alterations in major depression (Gögler et al., 2017; McIntyre et al., 2013). It is therefore possible that MDD participants' increased visual sensitivity to negative outcomes and blunted attention to positive scenarios were related to cognitive biases that may also compromise reward learning (Must et al., 2006).

Crucially, there were numerous significant group differences between depressed and healthy participants in their activation of anatomical ROIs implicated in reward during task-related events. However, it should be noted that these group differences did not include scenarios representing win/loss outcomes or anticipating those per se, hence deviating from prior evidence of anticipatory affect in MDD-related differences in reward processing (Smoski et al., 2018; Knutson & Greer, 2008; Sherdell et al., 2012). Instead, these group differences mainly pertained to neural activation during task-related events characterised by a reward prediction error whereby a positive (or negative) outcome occurred despite cues suggesting otherwise. More specifically, depressed patients displayed significantly increased activity in response to negative outcomes (loss) paired with negative RPE (e.g., 'Loss & no win in win'). Equally, MDD patients' responses in brain regions known to be innervated by dopaminergic neurons were markedly reduced when a positive outcome (win) was presented in combination with positive RPE (e.g., 'Win & no loss in loss') compared to healthy counterparts. Somewhat unexpectedly, baseline differences in nucleus accumbens activation, with the ventral striatum being a major neural substrate underlying the computation of RPE (Schultz et al., 1997, Schultz, 2000; Carlson et al., 2015), were modest at best. Medial orbitofrontal activation did not feature amongst significantly different ROI activations at all, contrasting with its previously found role in the feedback-loop supporting reward learning (Liu et al., 2011).

Activation clusters in the bilateral dorsal striatum, highlighting the putamen and to a lesser degree the caudate nucleus, differed most prominently between unmedicated MDD patients and healthy volunteers. Again, these group differences illustrated significantly increased responses to negative RPE ('No win in win') amongst depressed participants compared to healthy ones. Interestingly, cluster sizes for left putamen activation during 'No win in win'-scenarios notably exceeded patients' responses measured during 'Loss & no win in win'-events (241 versus 36 voxels, respectively). This specifically implies prediction error as the main feature delineating depressive computation of reward since 'amplified' negative RPE, compounded by a loss outcome in addition to the absence of anticipated win, did not exacerbate activational biases.

Considering the empirical link between basal ganglia (dys)function, its role in reward processing, and implications for anhedonic symptoms, the discussed neural alterations in MDD patients also align with their self-reports of anhedonia (Epstein et al., 2006; Treadway et al., 2012). Accordingly, unmedicated depressed participants reported their anhedonic severity as significantly greater than that in healthy controls, as measured by the SHAPS questionnaire. Meanwhile, these results correspond to the relation between anhedonia and diminished positive affect, illustrated by significantly lower self-reported positive affect amongst patients with MDD versus healthy volunteers (Werner-Seidler et al., 2014). Interestingly, neither greater anhedonic severity nor reduced positive affect in unmedicated depressed individuals was significantly correlated with their aberrant neural activation during reward processing at baseline. This may be attributed to the rather marginal baseline differences in nucleus accumbens activation between MDD patients compared to healthy controls given the accumbens' key role in anhedonic pathology (Liu et al., 2021; Schlaepfer et al., 2008). As the NAcc was not a major anatomical ROI marking baseline group differences, it would consequently not be expected to yield a strong correlation with anhedonia symptom severity.

In summary, the premise of reward learning and impairments thereof being driven by (dys)function of structures denoting the dopaminergic system has been further corroborated. This included validation of the probabilistic instrumental learning task (PILT) as a tool for assessing and neurally dissociating the anticipation versus consummation of a win/loss outcome as well as the cognitive computations that warrant prediction errors. The experimental hypothesis postulating baseline group differences between clinically depressed and healthy individuals in the activation of neural substrates underlying reward processing has also been confirmed. The following chapter will consider the effects of the NDRI-antidepressant drug bupropion on depressed patients in terms of neural activity and clinical symptoms of anhedonia.

Chapter 4:

Group differences between MDD patients & healthy controls in neural activation during reward processing and anhedonia symptomatology after 2 weeks of bupropion treatment

4.1. Introduction

In the previous chapter, baseline assessment of neural activation during reward processing in unmedicated depressed patients and healthy controls revealed numerous significant group differences pertaining to reward-related anatomical regions of interest. These activity clusters included the ventral and dorsal striatum, the right lateral OFC, as well as the left insula during task-related events. The present experimental chapter therefore studies the effects of a two-week treatment with the noradrenaline and dopamine reuptake inhibitor bupropion in MDD patients on neural activity at baseline compared to healthy controls. Given the association between dopaminergic activity and symptoms of anhedonia (Argyropoulos & Nutt, 2013), patients' neural changes during reward processing at test visit 2 will be related to self-reported measures of positive affect and anhedonia after bupropion treatment.

4.2. Objectives

The second experimental chapter's main objectives are as follows:

1) *Group differences*: Investigating the effect that two weeks of bupropion treatment for clinically depressed participants had on previously obtained group differences in neural activation at baseline compared to healthy controls.
2) *Relationship between neural activity & clinical outcomes*: Relating the potential change in neural activation amongst MDD patients to self-reported anhedonia & positive affect.

4.3. Hypotheses

1) *Group differences*: It is expected that two weeks of bupropion treatment in depressed participants reduced the significant group differences in striatal activation to reward measured at baseline when comparing healthy controls and MDD patients.
2) *Relationship between neural activity & clinical outcomes*: A hypothesised bupropion-induced increase in striatal activity during reward processing amongst depressed participants is expected to correlate with clinical improvements.

4.4. Participant demographics & change in sample size at test visit 2

Due to attrition or incomplete physiological noise recordings, group differences at visit 2 were investigated by analysing data from 79 instead of the original 85 participants at baseline (see Table 4.1. below).

Table 4.1. Breakdown of MDD patients and healthy controls tested on the reward task (PILT) at visit 2, displaying sex, mean age, and mean NART score for each group and overall sample.

	N (Sex)	Age (M ± SD)	NART (M ± SD)
Healthy controls	39 (26F, 13M)	30.54 ± 8.19	116.66 ± 4.91
MDD patients	40 (30F, 10M)	29.50 ± 9.07	115.93 ± 4.33
Total	79 (56F, 23M)	30.01 ± 8.66	116.19 ± 4.64

4.4.1. Participant characterisation at visit 2

For participant characterisation of medicated MDD patients and healthy controls in terms of their symptom severity at visit 2, self-report measures of MDD were taken (Table 4.2. below).

Table 4.2. Mean symptom severity, as measured by the HAM-D, SHAPS, and PANAS sub-scale for positive affect self-report questionnaires, for MDD patients and healthy volunteers at visit 2.

	HAM-D (M ± SD)	SHAPS (M ± SD)	PA scale (M ± SD)
Healthy controls	0.80 ± 1.16	20.41 ± 4.11	32.31 ± 7.17
MDD patients	10.53 ± 3.57	31.48 ± 5.36	20.70 ± 8.05

4.5. Group differences after two weeks of bupropion treatment in MDD patients

4.5.1. Results – Questionnaire findings

Running a repeated measures ANOVA showed a significant interaction effect between condition (HC versus MDD) and time (visit 1 versus visit 2) for mean scores on the SHAPS questionnaire, $F(1,77)=5.543$, $p=0.021$. This interaction effect is attributed to the administration of bupropion in depressed participants for two weeks. Accordingly, the medicated MDD group displayed a significant reduction in anhedonia, indicated by lower SHAPS scores, compared to patients at baseline prior to bupropion, $p=0.007$. The unmedicated healthy control group did not show this same reduction in SHAPS scores, $p=0.586$. Please see Table 4.2. for an overview of descriptive statistics for both groups. The main effect of condition, comparing HC and MDD participants was significant, $F(1,77)=170.166$, $p<0.001$, however, the main effect of time was not significant, $F(1,77)=2.483$, $p=0.119$. Mean scores and group differences on the SHAPS questionnaire for depressed patients and healthy controls at baseline, visit 2, for time difference (visit 2 – visit 1), respectively, are illustrated in Figure 4.1. below.

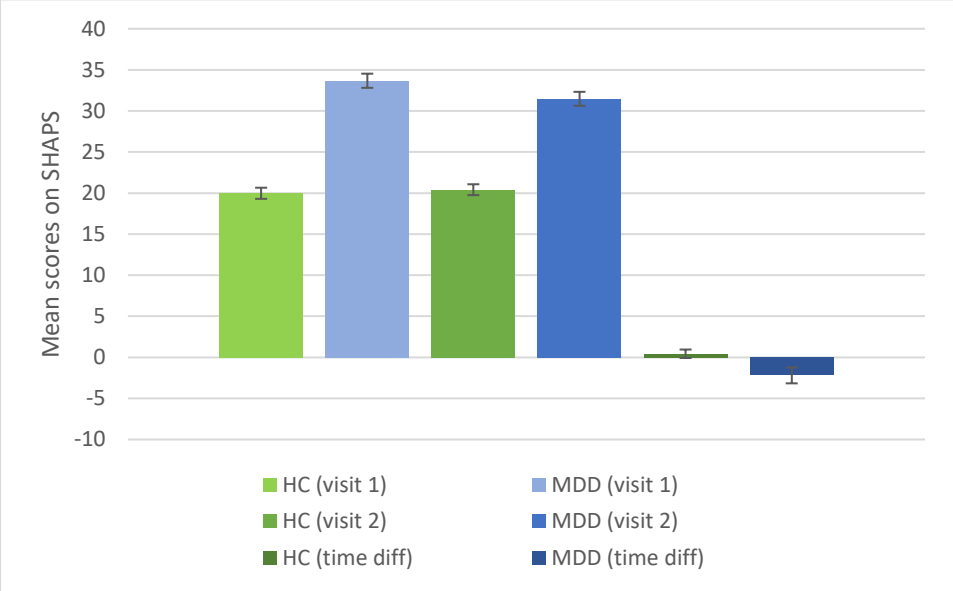

Figure 4.1. Summary overview of mean scores on the SHAPS questionnaire for depressed and healthy participants at baseline, visit 2, and time difference (visit 2 – visit 1). Error bars display standard error (SE).

Running a repeated measures ANOVA showed a significant interaction effect between condition (HC versus MDD) and time (visit 1 versus visit 2) for mean scores on the Positive Affect PANAS sub-scale, $F(1,77)=4.648$, $p=0.034$. This interaction effect is attributed to the administration of bupropion in depressed participants for two weeks. The medicated MDD group displayed an improvement in positive affect, indicated by increased PA sub-scale scores, compared to patients at baseline prior to bupropion, with a trend towards statistical significance, $p=0.082$. The unmedicated healthy control group did not show a significant change in PA scores, $p=0.200$. Please view Table 4.2. for a summary of descriptive statistics for both groups. The main effect of condition, comparing HC and MDD participants was significant, $F(1,77)=0.101$, $p<0.001$, however, the main effect of time was not significant, $F(1,77)=2.597$, $p=0.752$. Mean scores and group differences on the Positive Affect sub-scale for depressed patients and healthy controls at baseline, visit 2, for time difference (visit 2 – visit 1), respectively, are illustrated in Figure 4.2. below.

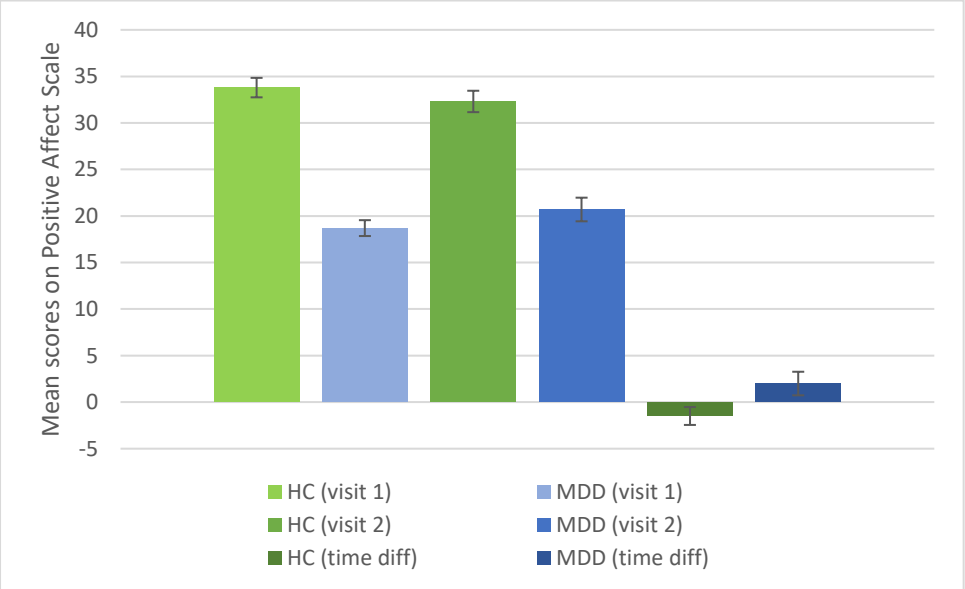

Figure 4.2. Summary overview of mean scores on the Positive Affect PANAS sub-scale for depressed and healthy participants at baseline, visit 2, and time difference (visit 2 – visit 1). Error bars display standard error (SE).

4.5.2. Results – Differences in neural activation at visit 2 only

Potential group differences between healthy controls and MDD patients were investigated at the whole-brain level. This yielded no statistically significant differences in neural activation to any of the PILT's task-related events at visit 2. In order to ascertain these findings, regions of interest analyses were carried out to examine both groups' neural responses for specified brain structures implicated in reward processing. The ROI analysis showed that the clinically depressed and the healthy control participants at visit 2 only did not significantly differ in neural activation for any pre-specified anatomical region of interest. None of those brain structures, comprising the ventral and dorsal striatum, insular cortex, and OFC, displayed a trend towards statistical significance either.

4.5.3. Time x group interaction effects

The investigation of time difference data at the whole-brain level revealed no significant group differences in neural activation for any of the 15 lower-level contrasts when comparing healthy controls and MDD patients. This was followed up by a regions of interest analysis. The resulting significant group differences are summarised in Table 4.3. below.

Table 4.3. Overview table of statistically significant group differences between healthy controls and MDD patients for pre-specified anatomical regions of interest at task-related events (lower-level contrasts) at visit 2 (time difference). Results were corrected for multiple comparisons by TFCE at FWE p=0.05.

Structure	Lower-level contrast	Direction of group comparison	Cluster size (voxels)	MNI (x,y,z)	t-score	*p*-value
Putamen (R)	No win in win	MDD > HC	2	28 0 -4	3.43	0.0470
Putamen (R)	Win – Neutral	HC > MDD	50	22 2 4	3.41	0.0310
Accumbens (R)	Win & no loss in loss	HC > MDD	1	8 6 -8	3.32	0.0376
Insula (L)	Win – Neutral	HC > MDD	8 3	-40 10 -10 -32 14 -14	3.62 3.28	0.0280 0.0420
Lateral OFC (R)	Win outcome	MDD > HC	2	28 46 -10	3.78	0.0474
Lateral OFC (R)	Win & no loss in loss	HC > MDD	10	40 38 -8	3.18	0.0332
Lateral OFC (R)	Loss & no win in win	MDD > HC	7	40 38 -8	3.18	0.0358

As shown in Table 4.3., conducting an ROI analysis on the time difference data that also accounted for subjects' performance at visit 1 did reveal some statistically significant group differences. Time interaction effects whose cluster size approximated or exceeded ten voxels were plotted to illustrate the trajectory and direction of group difference across visits 1 and 2, as well as the time interaction effect. Significant group differences with cluster sizes of less than five voxels will not be further discussed or interpreted due to lack of statistical robustness. With regards to neural activation at baseline, the right putamen for 'Win – Neutral outcome'-scenarios remained significantly different between the healthy and the clinically depressed group in terms of a time x group interaction effect, as displayed in Figure 4.3. The time interaction effect hence results from a significant increase in right putamen activation amongst MDD patients after bupropion treatment whereas healthy controls' neural activity decreased as a function of time.

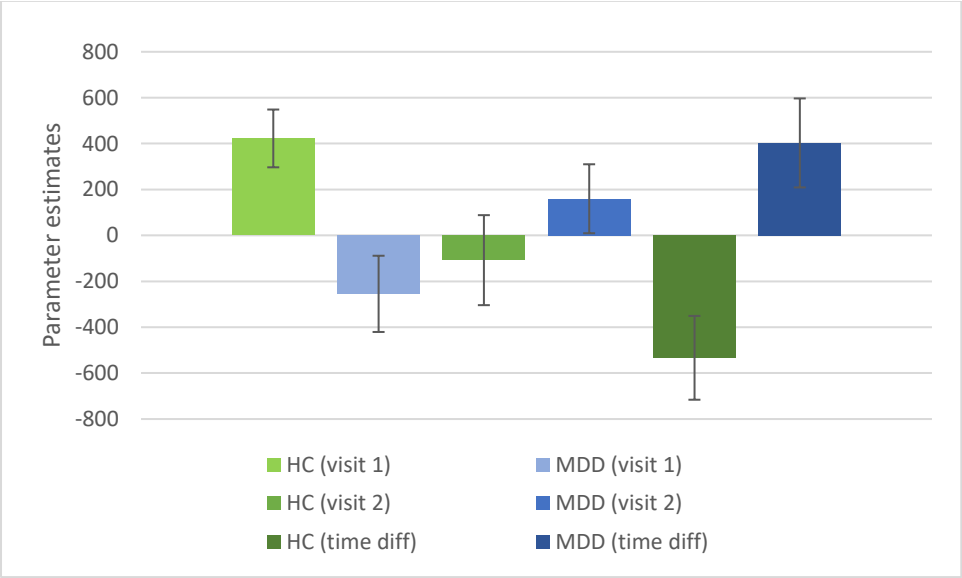

Figure 4.3. Overview figure of group differences between depressed individuals and healthy controls in right putamen activity (x y z = 22 2 4) during 'Win – Neutral outcome'-scenarios at visit 1, visit 2, and time difference (visit 2 – visit 1), respectively. Error bars display SE.

Further significant time interaction effects in neural activation during task-related events were obtained for the insular and lateral orbitofrontal cortices. For instance, left insular activity during 'Win – Neutral outcome'-scenarios demonstrated a time interaction effect whereby depressed patients' initially decreased response to 'Win – Neutral outcome'-events significantly increased after two weeks of bupropion treatment. Meanwhile, healthy individuals' left insular activation significantly decreased when considering their trajectory across both visits. This time interaction effect for both groups is illustrated in Figure 4.4. below.

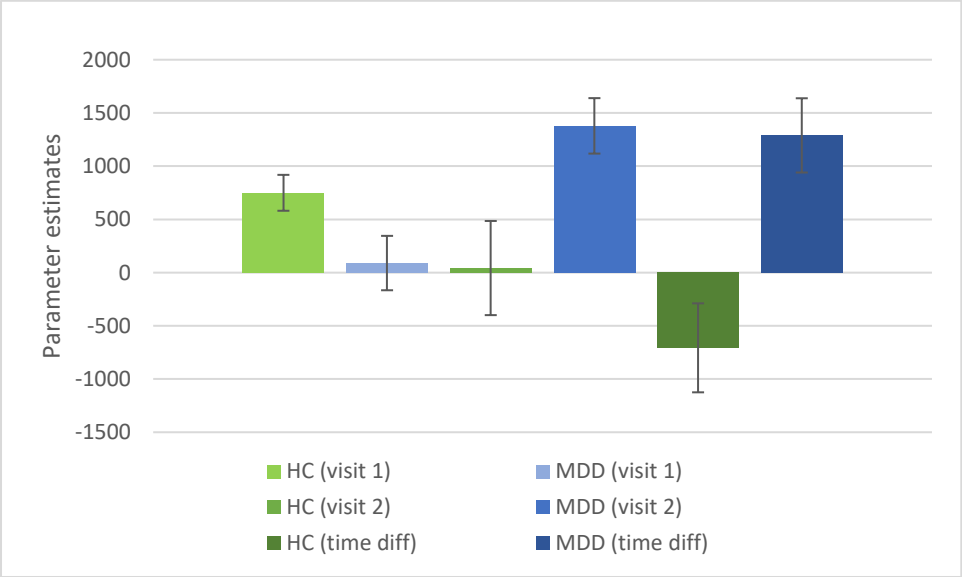

Figure 4.4. Overview figure of group differences between depressed individuals and healthy controls in left insular activity (x y z = -40 10 -10) during 'Win – Neutral outcome'-scenarios at visit 1, visit 2, and time difference (visit 2 – visit 1), respectively. Error bars display SE.

Neural activation in the right lateral OFC during 'Win & no loss in loss'-scenarios was marked by a significant time interaction effect in that depressed participants showed an increase in neural response after bupropion administration compared to significant reduction in activity at baseline. In contrast, healthy volunteers presented with a significant decrease in right lateral OFC activity during 'Win & no loss in loss'-events across test visits 1 and 2. Moreover, right lateral orbitofrontal activity during 'Loss & no win in win'-events denoted a significant time interaction effect, with MDD patients demonstrating a significant decrease in neural activity

after pharmacological treatment. Healthy controls' right lateral OFC activation in response to 'Loss & no win in win'-scenarios, however, significantly increased over time. Both time interaction effects for the right lateral OFC during 'Win & no loss in loss' and 'Loss & no win in win' are displayed in Figures 4.5. and 4.6., respectively.

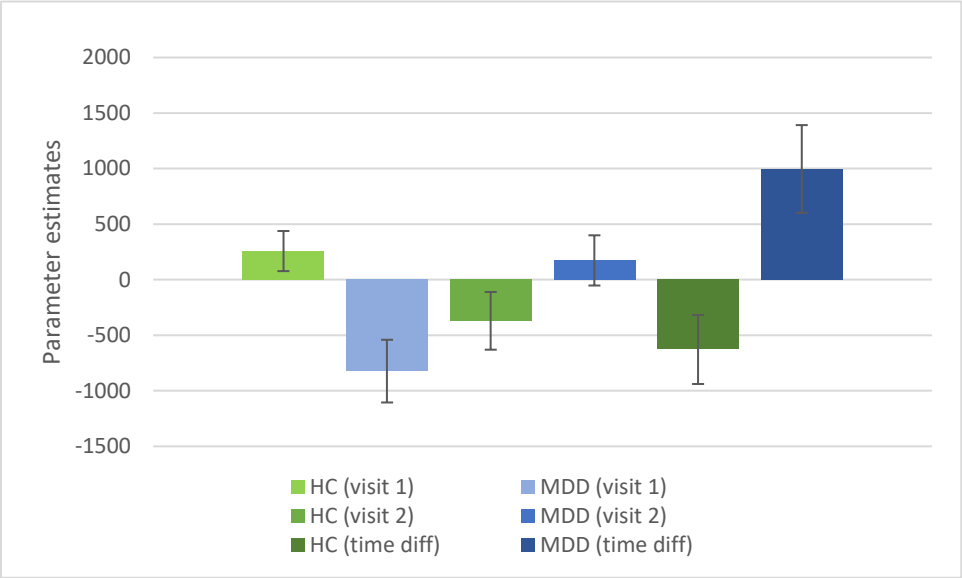

Figure 4.5. Overview figure of group differences between MDD patients and healthy controls in right lateral orbitofrontal activity (x y z = 40 38 -8) during 'Win & no loss in loss'-events at visit 1, visit 2, and time difference (visit 2 – visit 1), respectively. Error bars display SE.

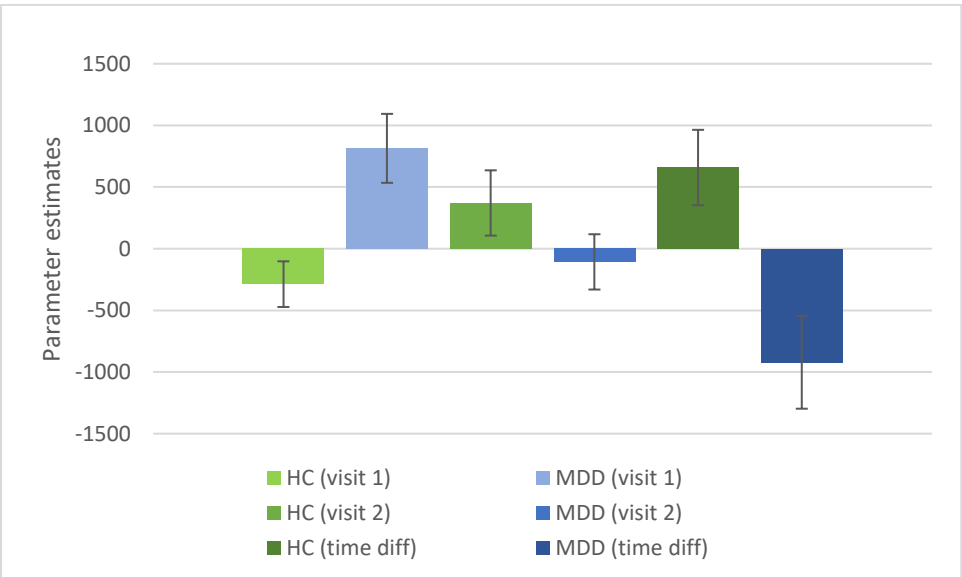

Figure 4.6. Overview figure of group differences between depressed individuals and healthy controls in right lateral orbitofrontal activity (x y z = 40 38 -8) during 'Loss & no win in win'-scenarios at visit 1, visit 2, and time difference (visit 2 – visit 1). Error bars display SE.

4.5.4. Relating time interaction effects in neural activity to anhedonia symptoms in MDD

It was subsequently addressed whether time interaction effects in neural activation during task-related events were associated with depressed participants' anhedonic symptom severity when comparing measures at baseline and after bupropion treatment. Thus, the significant time interactions for anatomical ROIs were correlated with patients' time difference scores (visit 2 – visit 1) on the SHAPS and PANAS sub-scale on Positive Affect, respectively. Resulting correlation coefficients (Pearson's r) and significance values are reported in Table 4.4.

Table 4.4. Correlation (Pearson's r) between MDD patients' parameter estimates for each anatomical ROI significant at time difference (visit 2 – visit 1) and time difference mean scores on the SHAPS and Positive Affect PANAS sub-scale questionnaires.

Anatomical ROI – Lower-level contrast	SHAPS (V2-V1; *p*-value)	PA sub-scale (V2-V1; *p*-value)
Putamen (R) – 'No win in win'	0.083; *p*=0.611	-0.047; *p*=0.772
Putamen (R) – 'Win – Neutral'	0.151; *p*=0.351	-0.219; p=0.175
Accumbens (R) – 'Win & no loss in loss'	0.076; *p*=0.642	0.026; *p*=0.875
Insula (L) – 'Win – Neutral'	0.393; *p*=0.012	-0.431; *p*=0.005
Lateral OFC (R) – 'Win outcome'	0.262; *p*=0.103	-0.262; *p*=0.102
Lateral OFC (R) – 'Win & no loss in loss'	0.191; *p*=0.238	-0.323; *p*=0.042
Lateral OFC (R) – 'Loss & no win in win'	-0.196; *p*=0.226	0.324; *p*=0.041

*corrected *p*-value

Statistically significant relationships between parameter estimates of anatomical ROIs and time difference mean scores on the SHAPS and Positive Affect PANAS sub-scale, indicated by Pearson's $r \geq 0.30$ and $p<0.05$, were then plotted to illustrate the nature of the correlation. There was a significantly positive relationship between MDD patients' left insular activity during 'Win – Neutral outcome'-scenarios at time differences and their decrease in SHAPS mean scores from baseline to visit 2 (Pearson's r=0.393, *p*=0.012; Figure 4.7.). Conversely, there was a significantly negative association between depressed patients' left insular activation during 'Win – Neutral outcome'-scenarios at time difference and their increase in Positive Affect mean scores from baseline to visit 2 (Pearson's r=-0.323, *p*=0.042; Figure 4.8.).

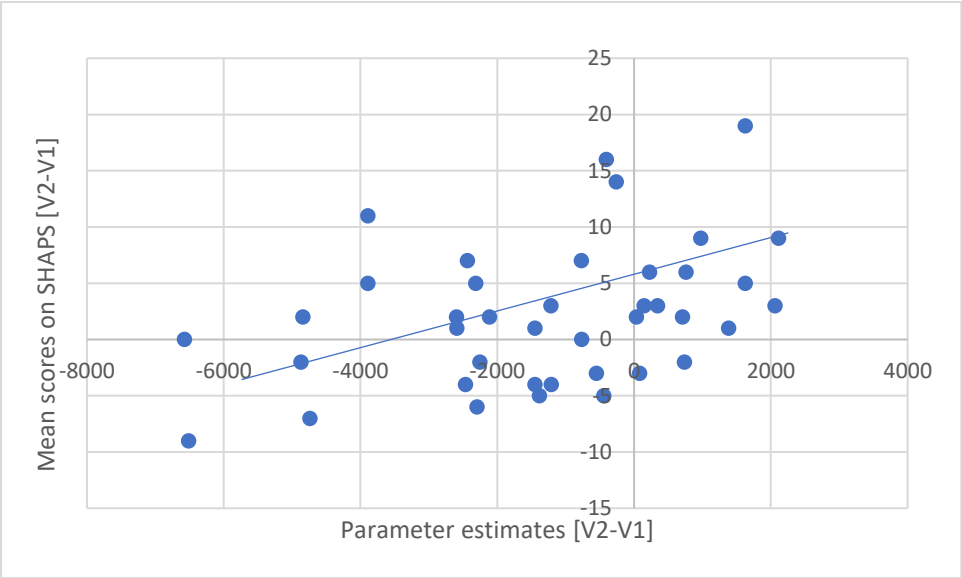

Figure 4.7. Significant positive relationship (Pearson's r=0.393, *p*=0.012) between MDD patients' left insular activity at 'Win – Neutral outcome' at time difference (visit 2 – visit 1) and MDD time difference scores on the SHAPS questionnaire.

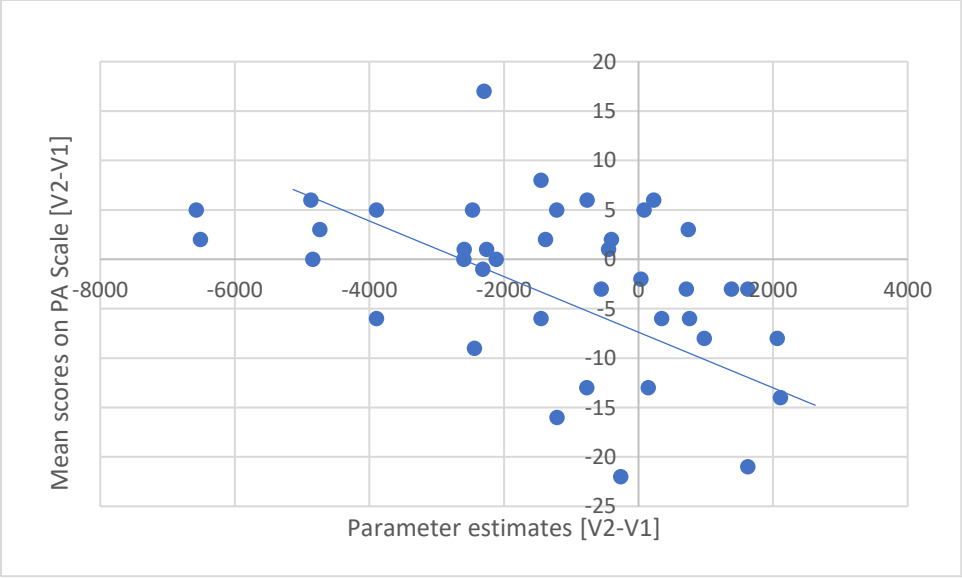

Figure 4.8. Significant negative relationship (Pearson's r=-0.431, *p*=0.005) between MDD patients' left insular activity at 'Win – Neutral outcome' at time difference (visit 2 – visit 1) and MDD time difference scores on the Positive Affect PANAS sub-scale.

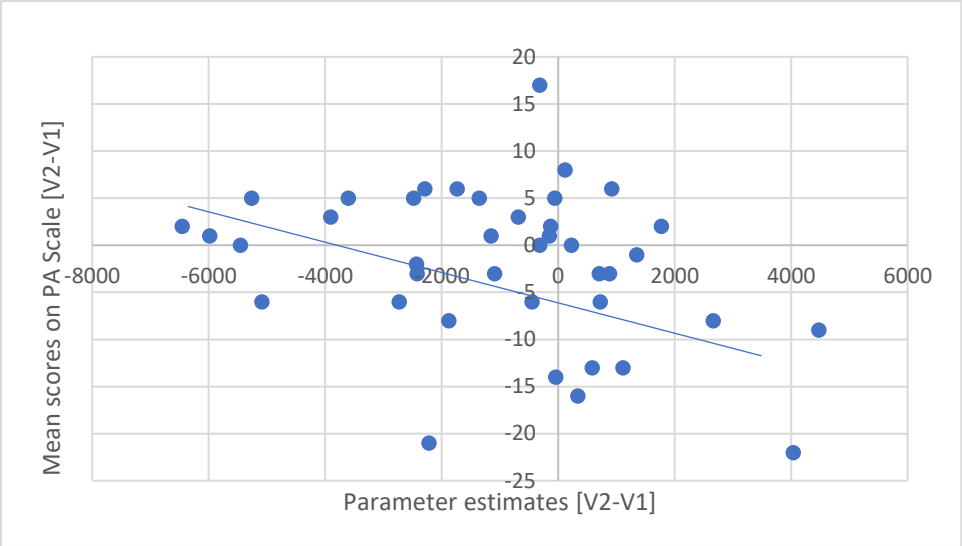

Figure 4.9. Significant negative relationship (Pearson's r=-0.323, *p*=0.042) between MDD patients' right lateral orbitofrontal activity at 'Win & no loss in loss' at time difference (visit 2 – visit 1) and MDD time difference scores on the Positive Affect sub-scale.

Moreover, there was a negative relationship between MDD patients' right lateral orbitofrontal activity during 'Win & no loss in loss'-events at time difference and their increase in Positive Affect mean scores from baseline to visit 2 (Pearson's r=-0.323, *p*=0.042; Figure 4.9. above). The correlation between depressed patients' right lateral orbitofrontal activation during 'Loss & no win in win'-scenarios at time difference and their increase in Positive Affect mean scores from baseline to visit 2 was significantly positive (Pearson's r=0.324, *p*=0.041; Figure 4.10.).

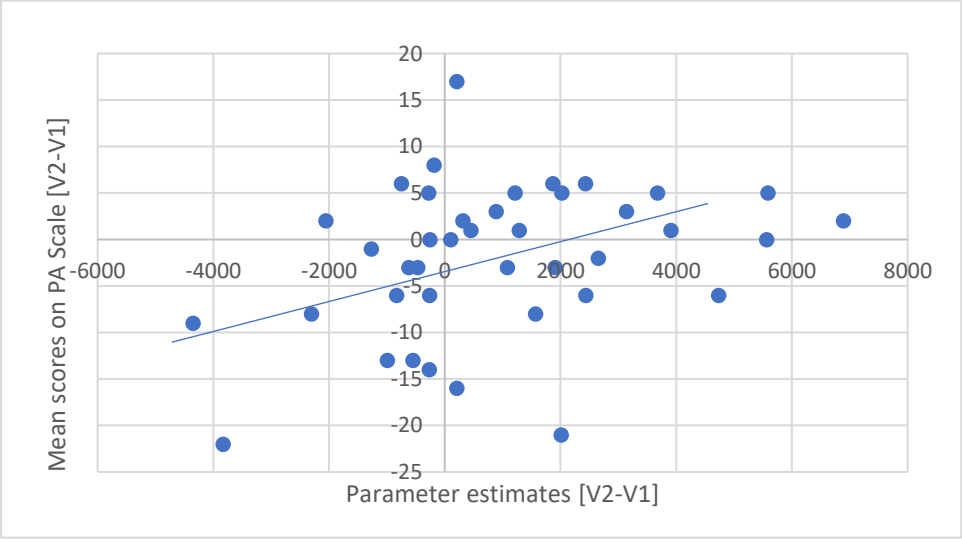

Figure 4.10. Significant positive relationship (Pearson's r=0.324, *p*=0.041) between MDD patients' right lateral orbitofrontal activity at 'Loss & no win in win' at time difference (visit 2 – visit 1) and MDD time difference scores on the Positive Affect sub-scale.

4.6. Summary of findings

Examining data obtained at test visit 2, after two weeks of bupropion treatment in MDD patients, revealed no significant group differences in neural activation during reward processing at the whole brain nor ROI level between clinically depressed and healthy participants. Investigating the time difference between both test visits for each group, however, yielded several significant time interaction effects in anatomical regions of interest. These ROIs included the right putamen, left insular, and right lateral orbitofrontal cortices.

A repeated measures ANOVA on anhedonic symptom severity, as measured by the SHAPS and PANAS sub-scale for positive affect, in MDD patients and healthy controls yielded a significant interaction effect between condition (group) and time. Mean scores on the SHAPS questionnaire showed a significant reduction in anhedonia amongst depressed individuals after bupropion treatment compared to their unmedicated baseline measures. Unmedicated healthy controls did not report a change in symptoms of anhedonia, albeit significantly lower than that measured in MDD patients. PANAS sub-scale scores on positive affect indicated an improvement in depressed individuals' anhedonic symptoms after bupropion treatment compared to baseline with a trend towards statistical significance. The main effect of condition in Positive Affect scores was significant whereby MDD participants displayed significantly lower positive affect than did healthy volunteers. The main effect of time was not statistically significant.

Relating the time interaction effects in neural activation to depressed patients' change in clinical symptom severity demonstrated significant relationships between brain activity and anhedonia. An increase in left insular activation in MDD patients from baseline to visit 2 (after bupropion) during 'Win – Neutral outcome'-scenarios was significantly correlated with a decrease in anhedonic symptoms and increase in positive affect, suggested by SHAPS and PA sub-scale, respectively. Additionally, depressed participants' bupropion-related increase in right lateral

OFC response to ‘Win & no loss in loss’ was negatively associated with an increase in their positive affect scores, measured by the PANAS sub-scale. MDD patients’ decrease in right lateral OFC response during ‘Loss & no win in win’-scenarios was significantly positively correlated with improvements in positive affect (PANAS sub-scale).

4.7. Discussion

The second experimental chapter sought to investigate the effects of a two-week treatment with the NDRI-antidepressant drug bupropion on depressed patients’ neural activation during reward processing. Corresponding to evidence suggesting enhanced dopaminergic activity as a promoter of improvements in reward processing, it was assumed that administering bupropion would help reduce baseline group differences in DA system activity between MDD and healthy participants. Indeed, there were no significant group differences found at visit 2 at the whole-brain or ROI level, showing that two weeks of bupropion treatment yielded a normalisation in initially aberrant neural activation during task-related events. This confirms the first experimental hypothesis of this chapter (4.3.1.) and corroborates the dopamine system’s role in reward, alongside noradrenergic activity (Peciña et al., 2003; Wyvell & Berridge, 2000).

Moreover, analyses revealed multiple significant time interaction effects between condition (MDD/HC group) and time (baseline compared to post-bupropion treatment). These interaction effects pertained to the right putamen and left insular cortex during ‘Win – Neutral outcome’-events whereby neural activation increased amongst depressed participants after bupropion treatment whereas healthy controls’ activity in those ROIs decreased over time. A similar pattern for both groups, respectively, was observed in the right lateral OFC for ‘Win & no loss in loss’-scenarios. Right lateral orbitofrontal activation during ‘Loss & no win in win’-events, however, was marked by significantly decreased neural activation in MDD patients after bupropion treatment whilst healthy volunteers’ activity increased between visits. These results correspond to prior evidence and current experimental hypotheses, postulating that depressed

patients' aberrant neural activation in response to positive or negative reward scenarios would change upon receiving the pharmacological intervention. Thus, their neural sensitivity to positive events improved over time while biased responses towards negative loss scenarios at baseline could be reduced with bupropion. Nevertheless, significant interaction effects, denoted by healthy participants' change in brain activation during task-related events were not expected precisely because no experimental intervention was implemented that would have otherwise warranted controls' time-related change in neural activation during reward processing. This observation is hence attributed to effects of repeating the reward task, a study limitation that will be discussed in the following chapter.

As noted in 4.3.2., it was further hypothesised that normalisation of dopaminergic activity in depressed participants with bupropion would coincide with an improvement in their self-reported severity of anhedonia as well as positive affect compared to baseline. Findings obtained at test visit 2 did align with this prediction, illustrated by a significant reduction in anhedonic symptom severity as measured by the SHAPS questionnaire. MDD patients' scores on the PANAS sub-scale for positive affect additionally indicated improvements thereof, shown by a trend towards statistical significance when compared to baseline. This corresponds to research on the relationship between (dys)function of the DA system and clinical depression, potentially relating to anhedonia in particular (Stein, 2008). As expected, healthy controls' measures of anhedonia or positive affect did not change over time.

Furthermore, MDD patients' changes in self-reported symptoms of anhedonia and positive affect, respectively, correlated with their time-related changes in neural activation. As described in the previous section of this chapter (4.6.), enhanced right lateral orbitofrontal activation during positive RPE ('Win & no loss in loss') was found to negatively correlate with improved positive affect. Likewise, reduction in right lateral OFC activation during negative RPE ('Loss & no win in win'-events) was found to be positively correlated with an increase in depressed participants' positive affect. These results point towards the relevance of aberrant reward

learning within major depression in terms of the computation of reward anticipation versus actual outcome, hence denoting reward prediction error (Husain & Roiser, 2018). Accordingly, MDD patients' baseline hyperactivation of the lateral OFC during negative prediction error signals corresponds to the bupropion-induced decrease thereof alongside symptomatic improvements in positive affect (Rouhani & Niv, 2019). Meanwhile, depressed participants' increase in right lateral orbitofrontal activity in response to positive RPE-scenarios was negatively correlated with improved positive affect. This alludes to an initial, bupropion-induced blunting of the reward signal during RPE processing, which, as mentioned in 1.5.4., is particularly common during the early phase of antidepressant drug treatment, including effects specific to bupropion (Kumar et al., 2018; Walsh et al., 2018). Hence, neural changes temporally precede measurable cognitive and symptomatic improvements. Both findings are consistent with the literature on RPE as a central computational marker of MDD pathology and substantiate RPE as a cognitive target for treating reward-related impairments in anhedonic depression (Ubl et al., 2015).

Lastly, analyses also yielded a significant correlation between bupropion-induced increases in left insular activation during positive outcomes ('Win – Neutral') and symptomatic changes post-treatment. Increased left insular activation was significantly positively correlated with a decrease in anhedonia symptoms whereas a negative association was found for normalised insular response and improved positive affect. These results appear inconclusive. It may be argued that insular activation is predominantly associated with processing aversive information (Garrison et al., 2013), therefore aligning with its increase being negatively correlated with improved positive affect. Conversely though, enhanced neural activation during the computation of positive outcomes, as given here, would favour the positive relationship with reduced symptom severity of anhedonia post-bupropion. The above discussed findings in depressed individuals' reward processing obtained after bupropion treatment are thus further contextualised and appraised with regards to experimental limitations in the following chapter.

Chapter 5:

General discussion

This thesis sought to investigate the effects of the NDRI-antidepressant drug bupropion on neural activation during reward processing in clinically depressed patients compared to healthy control subjects after establishing baseline differences between both groups. This was addressed by studying participants' neural responses whilst completing multiple trials of a probabilistic instrumental learning task (PILT) to examine how computing negative versus positive reward scenarios would differ between groups on a neural level. Bupropion-induced changes in anhedonic severity and their relevancy to normalisation of MDD patients' aberrant reward processing were reported as well.

5.1. Summary of main findings

5.1.1. Baseline differences between MDD patients & healthy volunteers

Chapter 3 primarily considered baseline differences between unmedicated depressed and healthy individuals. Initially, the main effect of task corroborated the PILT's validity for assessing neural activity patterns associated with reward processing in response to task-related events. It did so by revealing significant mean activation in brain regions comprising the mesocorticolimbic pathway across all participants, hence corresponding to prior research on neural substrates underlying positive and negative reward (see Figure 5.1.). Subsequently, significant group differences between unmedicated MDD patients and healthy volunteers in their neural responses to positive versus negative reward scenarios were obtained, both at the whole-brain level and for pre-specified anatomical regions of interest.

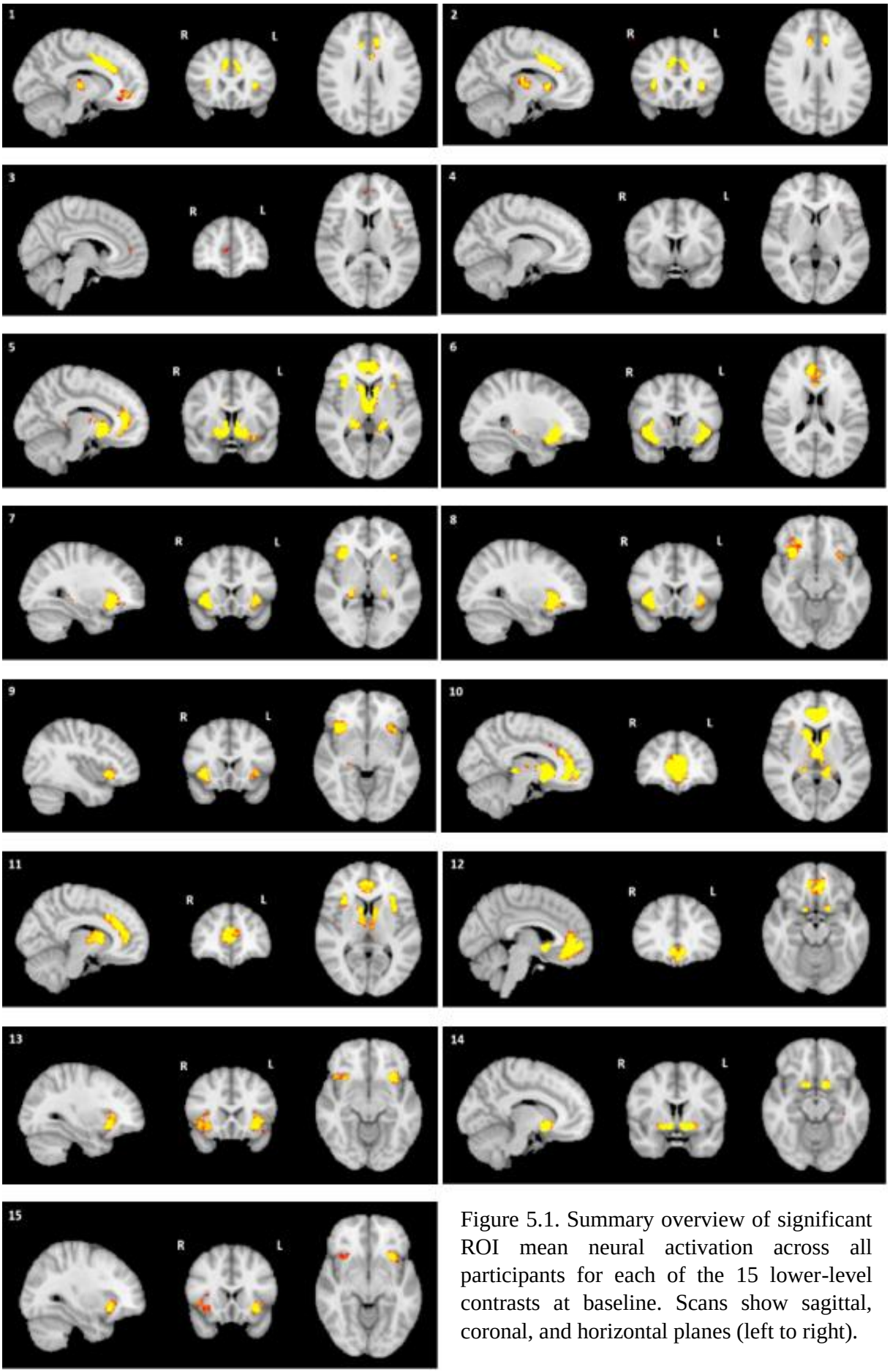

Figure 5.1. Summary overview of significant ROI mean neural activation across all participants for each of the 15 lower-level contrasts at baseline. Scans show sagittal, coronal, and horizontal planes (left to right).

Group differences consistently showed depressed participants' greater responsiveness during negative reward scenarios whereas their brain activity appeared significantly reduced when computing positive reward scenarios compared to healthy counterparts. Whilst these WBA findings were limited to neural areas involved in visual processing, the ROI results reflected the same effect in reward-related structures. Accordingly, MDD patients' neural responses to events denoted by negative reward prediction error (RPE) such as 'No win in win' and 'Loss & no win in win' were marked by increased activation in the bilateral dorsal striatum, the right ventral striatum (accumbens), and insular cortex. The depressed group's activity in these anatomical regions implicated in reward during 'Win & no loss in loss', representing a positive reward scenario, however, was found to be significantly lower than that observed in healthy controls.

In terms of symptomatic severity, unmedicated depressed patients displayed, as expected, significantly greater severity of overall MDD (HAM-D), anhedonia (SHAPS), and lower positive affect (PANAS sub-scale), respectively, than did healthy participants. Those symptomatic group differences were not significantly correlated with measures of neural activation in the depressed sample.

5.1.2. Group differences after two weeks of bupropion treatment in MDD patients

Examining the fMRI data obtained after two weeks of bupropion treatment in MDD patients yielded no significant group differences in neural activation during reward processing at the whole brain nor ROI level between clinically depressed and healthy participants. However, accounting for the time difference between both test visits did reveal some significant time interaction effects in anatomical brain regions associated with reward, including the right putamen, left insular, and right lateral orbitofrontal cortices.

A repeated measures ANOVA on anhedonic symptom severity also showed significant interaction effects between time and group. Mean scores on the SHAPS questionnaire showed a significant reduction in anhedonia amongst depressed individuals after bupropion treatment compared to their unmedicated baseline measures. Healthy volunteers did not report a change in symptoms of anhedonia over time, however, their anhedonia scores were significantly lower than those measured in MDD patients. PANAS sub-scale scores on positive affect indicated an improvement in depressed individuals' anhedonic symptoms after bupropion compared to baseline with a trend towards statistical significance. The main effect of condition in Positive Affect scores was significant whereby MDD participants displayed significantly lower positive affect than did healthy volunteers. The main effect of time was not statistically significant.

Relating the time interaction effects in neural responses to depressed patients' change in clinical symptom severity demonstrated significant relationships between brain activity and anhedonia. An increase in left insular activation in MDD patients from baseline to visit 2 (after bupropion) during 'Win – Neutral outcome'-scenarios was significantly correlated with a decrease in anhedonic symptoms and increase in positive affect, suggested by SHAPS and PA sub-scale, respectively. Additionally, augmented right lateral orbitofrontal response to win in depressed participants was associated with lower increases in positive affect. Meanwhile, MDD patients' decrease in right lateral OFC response during loss scenarios was significantly positively correlated with improvements in positive affect, measured by the PANAS sub-scale.

5.2. Main findings in context

The extensive mean activation of key nodes within the mesocorticolimbic system in response to positive and negative reward scenarios was accompanied by results whose implications are manifold. Most broadly, application of the PILT illustrates the mesocorticolimbic pathway's role in reward processing, thereby extending a large cohort of literature on the neurophysiology of reward (Schultz, 2000; Sescousse et al., 2013). Moreover, the mean activity pattern

demonstrates the dissociation between win (reward) and loss (punishment) in terms of differential brain activation clusters in response to specific task-related events. Mean insular activity featured more prominently in trials representing loss, corroborating its function in processing aversive information, including punishment (i.e., loss) (Straube & Miltner, 2011; Palminteri et al., 2012). Activation of the insular cortex was also shown in response to prediction error trials, indicated by incongruent anticipation versus consummation of reward outcomes, thus reinforcing prior evidence on the insula's importance for computing RPE (Preuschoff et al., 2008; Bossaerts, 2010). Analyses additionally revealed striatal responses as the predominant neural basis underlying reward anticipation whilst mean orbitofrontal activation appeared most pronounced during participants' 'consummation' of reward outcomes. Importantly, by methodologically distinguishing between anticipating and experiencing an outcome, as well as the discrepancy between both (RPE), the reward task helped delineate the neural substrates that underpin these cognitive computations. This is critical for facilitating a better grasp of the biological mechanisms of reward processing and how their malfunction may instigate and sustain anhedonic symptoms as seen in MDD.

Chiefly, there were broad differences between depressed and healthy participants in neural activation of the mesocorticolimbic circuit, however, group differences in brain activity were not prominent in the ventral striatum. As described in previous studies, the anhedonia-related impairments associated with major depression are thought to pertain to aberrant reward learning (Vrieze et al., 2013; Rømer Thomsen, 2015; Huys et al., 2013). They hence point towards depressed individuals' difficulties with appraising stimuli that are predictive (anticipation) versus the actual experience (i.e., consummation) of an outcome. These earlier findings are clearly replicated in the current study whereby group differences between healthy and depressed participants in their brain activation were most strongly shown during task-related events denoted by either positive or negative prediction error. Additionally, such group differences extended to significantly different responses based on the affective valence of task-related

events, with increased neural activation to loss alongside decreased activity during win scenarios amongst MDD patients, respectively. Both effects correspond to the behavioural symptomatology of major depression, showing negatively biased processing, reduced positive affect, and allude to depressed individuals' loss of pleasure derived from positive experiences (Nelis et al., 2015; Werner-Seidler et al., 2014).

In accordance with this established phenomenology of MDD, patients displayed significantly greater severity of anhedonia alongside diminished positive affect than healthy controls. Given the association between anhedonia and aberrant activity of the basal ganglia, with the nucleus accumbens in particular, the symptomatic and neural differences would have been expected to be strongly correlated (Keedwell et al., 2005; Segarra et al., 2016). However, in contrast to prior research, no significant correlation between altered brain activation in unmedicated MDD patients and their anhedonic symptom severity or diminished positive affect was reported. The nucleus accumbens is a key neural substrate underlying clinical anhedonia so it would have been thought to feature amongst major activation clusters altered in the depressed sample to yield a strong association with anhedonic severity (Liu et al., 2021; Schlaepfer et al., 2008). One possible explanation for the lack of correlation may hence be the statistically negligeable baseline group differences in ventral striatal activity during reward processing between depressed and healthy participants obtained in this study. Symptomatic and neural differences were subsequently investigated after a two-week-period of bupropion treatment in the depressed group.

Bupropion acts as a dual reuptake inhibitor of both dopamine and noradrenaline. In line with dopamine's extensively described role in reward learning, the antidepressant drug's pharmacological profile warranted a general normalisation of MDD patients' brain activation when performing on the PILT at test visit 2. Consequently, measuring both groups' mean brain activity at test visit 2 only did not yield significant differences in neural responses to positive

or negative reward scenarios between depressed and healthy individuals. The statistically significant time interaction effects, however, were not expected based on the lack of experimental intervention delivered to healthy participants. These results therefore encourage further investigation into practice effects, as well as other possible factors influencing the control group's performance observed here, with suggestions outlined in section 5.5. of this chapter. By virtue of enhancing basal ganglia function and due to bupropion's antidepressant properties, it was anticipated that anhedonic severity in MDD patients would significantly decrease, which was found, whilst their self-reported positive affect improved, too (Cooper et al., 2018; Irvin et al., 2020). Several significant correlations between depressed participants' symptomatic changes in anhedonia and positive affect, respectively, and time-related differences in neural activation were obtained.

First, MDD patients' decrease in right lateral OFC activity during negative RPE was correlated with greater increases in positive affect. This relates to the negatively biased processing ascribed to major depression whereby patients tend to pay more attention to negative relative to positive stimuli (Gotlib et al., 2004). As the OFC accommodates a neural representation of reward in terms of integrating predictive information relevant for reward learning, its increased response to loss at baseline would explain compromised positive affect (Peters & Büchel, 2010; Klein-Flügge et al., 2013). Decreased orbitofrontal activation during loss after bupropion treatment in correlation with greater improvements in positive affect hence aligns with the research on both aversive processing and RPE in major depression (Rouhani & Niv, 2019).

Interestingly though, MDD patients' time-related increase in right lateral OFC activation during positive RPE was associated with lower increases in their positive affect. According to the above-described account on why decreased OFC response would relate to greater improvements in positive affect, one may have expected enhanced orbitofrontal activity to win as a promoter of positive affect. That the present finding contrasts with this may hint at the

OFC's role in affective regulation so that significant activity changes, despite augmented response to positive reward, may have some acute negative effects on symptomatic outcomes nonetheless (Golkar et al., 2012; Bremner et al., 2002). On this point, it is worth highlighting the brief duration of patients' medication treatment implemented in this study which, as explained in 1.5.4. of chapter 1, only grants a limited insight into bupropion's clinical effects (see study limitations discussed in Section 5.4.1. of this chapter). Besides, decreased orbitofrontal activation during negative reward (i.e., loss) scenarios has previously been found to positively correlate with greater severity of depressive symptomatology (Jin et al., 2017), however, this observation was not made over time in medicated individuals as done here.

Furthermore, depressed participants' increased left insular activation in response to win was also associated with lower increases in positive affect. This could refer to the insular cortex as a key neural substrate that has been linked to aversive processing, illustrated by its negative association with positive affect (Liu et al., 2011). Such a generalised account, however, is incongruous with the result that MDD patients' larger increases in left insular response to reward coincided with a greater reduction in anhedonic symptom severity. The former explanation would rely on the assumption that insular activation *in general* pertains to negative processing, hence correlating enhanced insular activation *overall* to diminished improvements in positive affect. Meanwhile, the latter result would postulate that the insula's function in anhedonia is a directional, arguably more nuanced one whereby its activity during negative/loss scenarios specifically would be indicative of patients' symptomatic status – not necessarily neural responses measured during positive reward. Although anhedonia and lack of positive affect do not constitute identical concepts, they do overlap, thus emphasising the inconclusive nature of both relationships between enhanced insular activity and its implications for depressed individuals' symptomatic changes. Further investigation into the evidence discussed here is therefore warranted.

5.3. Clinical implications

Collectively, the results presented in this thesis demonstrate that the NDRI-antidepressant drug bupropion normalised depressed individuals' altered brain activation during reward processing. Facilitating these significant changes after merely two weeks of treatment suggests bupropion as a promising pharmacological approach for rectifying neural anomalies commonly associated with MDD. Its clinical use is further supported by significantly reducing anhedonic symptom severity and some improvements in patients' positive affect, including important implications for the role of dopamine (and noradrenaline) in computing reward. Moreover, the significant correlations between bupropion-induced activity changes and some anatomical ROIs and enhanced self-reported anhedonia and positive affect across test visits allude to the mechanistic relevancy of neural changes for instigating symptomatic ones. Specifically, it may point towards activational changes in disorder-related brain regions as possible predictors of a drug's clinical efficacy in treating the respective psychiatric illness.

5.4. Study limitations

5.4.1. Study design & testing the experimental effects of bupropion

Despite the merit of the insights obtained by the present study, such as its relatively large sample size, there are some methodological and experimental limitations to be addressed. First, this study would have ideally implemented a double-blind, randomised, placebo-controlled design whereby both groups, depressed patients and healthy volunteers, received either bupropion treatment or an inactive pill as placebo. Doing so would have ascertained that results are attributable to experimental effects of the drug's pharmacological profile whilst ruling out alternative accounts such as placebo and time effects on performance. This holds

especially true within the context of changes in clinical symptoms of anhedonia and positive affect amongst MDD patients when comparing baseline reports to measures after two weeks of bupropion treatment. Relating specific bupropion-induced changes in depressed participants' subjective well-being to time interaction effects in neural activation during reward processing may have thereby been more scientifically robust.

Additionally, administering bupropion or placebo capsules in non-depressed individuals may have granted informative insights into their responsiveness to pharmacological manipulation of their dopaminergic (and noradrenergic) activity on reward processing. Corresponding observations may have allowed a more comprehensive understanding of bupropion's neural effects. Whilst bupropion (or placebo) administration in healthy volunteers would have been permissible, randomly allocated treatment with either an active antidepressant drug or a placebo pill in depressed participants raises ethical concerns and was therefore decided against. Moreover, adopting a double-blind, randomised, placebo-controlled design would have notably increased the study's complexity, hence suggesting a future investigation into bupropion's effects to complement the findings obtained here.

5.4.2. Statistical stringency & methodological issues of fMRI

Further to the above, the statistical analysis of neural data followed a very rigorous approach to determining statistical significance levels. Accordingly, it can be argued that absence of significant findings, whether in terms of group differences or otherwise, is not necessarily proof that no differences or neural activation during task-related events were given. The strict cut-off point adhered to in this study served to increase statistical robustness. However, conducting analyses with a more liberal approach may have improved the nuance of reported results since

a trend towards statistical significance may still reveal neural patterns that might be indicative of depressive tendencies and endophenotypes. Identifying such tendencies may permit early detection of individuals' disposition to (anhedonic) MDD and thus, facilitate preventative intervention. This also points towards a wider debate around the strengths and limitations to neuroimaging techniques as tools for acquiring indirect markers of behavioural pathology.

Importantly, it is worth noting that the reward learning task used in this study only offers limited ecological validity for operationalising reward processing in major depression and its implications for patients' subjective experience. Namely, the pathological deficits reported by depressed individuals largely pertain to social reward and their diminished ability to engage in such, alongside feelings of social rejection and withdrawal (Pegg et al., 2021). As patients tend to lack motivation to seek out social interaction, this often has detrimental effects on their personal relationships. Whilst monetary reward tasks such as a the PILT provide valuable computational tools for inferring reward sensitivity and responsiveness, they arguably lack the social specificity associated with anhedonic symptomatology in MDD (Zhang et al., 2020). It therefore appears critical to not overlook or exclude social measures of reward processing when developing and administering cognitive-behavioural tools for assessing reward-related impairments in anhedonia (Ait Oumeziane et al., 2019).

Lastly, it could have been advantageous to relate the neural substrates activated during reward processing to behavioural or performance measures on the reward task. This would have enhanced the translatability of mechanistic brain activity to behavioural outcomes on a cognitive level, and was addressed on the same data set by Walsh (2016).

5.5. Future directions

As mentioned in 5.3., pharmacologically induced changes in neural activation during cognitive processing may permit valuable predictions of a given drug's clinical efficacy in alleviating (MDD) symptoms. This proposes the examination of neural responsiveness to various drug treatments as a possible early marker of individual differences in antidepressant efficacy, a widely reported challenge in psychiatric healthcare. Additionally, it is worth rectifying the current study's limitations regarding its experimental design. Implementing a double-blind, randomised, placebo-controlled design involving drug administration in both depressed and healthy participants would hence supplement present findings and further our grasp of bupropion's neural and behavioural effects. Importantly, doing so would help elucidate the nature of the time x group interaction effects which also showed changes in neural activation amongst healthy volunteers despite not receiving experimental intervention between test visits. At this stage, it is difficult to determine whether the unexpected interaction effects in neural responses to the task's reward-related events are attributable to bupropion's pharmacological profile, regression to the mean, or clinically relevant differences in reward learning.

Concerning bupropion's clinical effectiveness, it may also be interesting to undertake a direct comparison between antidepressant effects and those achieved by means of Behavioural Activation Therapy given the latter's potential for treating anhedonia. For instance, Chen et al. (2021) exposed participants to positive scenes, followed by imaginal recounting to reinforce the positive mental images induced by the previously viewed stimuli. They reported significant self-reported decreased negative affect in MDD patients in addition to enhanced positive affect. Although these findings only constitute preliminary pilot data thus far, they do lend support to BAT as a supplementary treatment in addition to – and beyond – conventional CBT or pharmacotherapy, especially for those suffering from anhedonia. The above suggestions, however, are arguably most viable within the context of longer-term or longitudinal studies whose duration exceeds the two-week period implemented here.

5.6. Conclusion

This thesis sought to elucidate the reward circuitry in terms of its aberrant function implicated in the behavioural pathology seen in major depressive disorder. This was endeavoured by first establishing baseline group differences between unmedicated depressed patients and healthy controls in their neural activation whilst performing a reward learning task. Corresponding fMRI results and self-reported severity of anhedonia and impairments in positive affect aligned with the literature on anomalous neural and symptomatic measures of reward in MDD. These task-related neural alterations in the clinically depressed sample were normalised after two weeks of bupropion treatment compared to unmedicated healthy volunteers. Neural changes also coincided with bupropion-treated MDD patients' symptomatic improvements in anhedonia and positive affect, including some time interaction effects whose neural and cognitive underpinnings require further examination. The obtained findings have important implications for the role of dopamine in reward processing, how its impairments pertain to clinical anhedonia, and the use of dopaminergic antidepressant drugs as promising therapeutic targets for treating neural correlates and cardinal symptoms of major depression.

APPENDIX A

Table A. Summary table of higher-level mean neural activation clusters across both groups at the whole-brain level in response to task-related events (lower-level contrasts). Results were corrected for multiple comparisons by TFCE at family-wise error (FWE) rate p=0.05.

Lower-level contrast	Cluster size (voxels)	MNI (x,y,z)	t-score	*p*-value	Structure
Win anticipation – baseline	26927 7249 30	-30 -74 -14 40 -44 -22 -14 -22 4	3.61 4.39 6.75	<0.001 <0.001 0.022	Occipital cortex, extending into middle temporal gyrus & frontal pole, precentral gyrus, opercular cortex (1) Bilateral putamen, extending into bilateral pallidum, putamen and left thalamus (2) Anterior cingulate gyrus (3)
Loss anticipation – baseline	27714 8778 27 7	-32 -74 -14 40 -48 -20 -4 -28 -4 16 -18 60	3.24 4.00 7.01 2.94	<0.001 <0.001 0.020 0.049	Precentral gyrus, extending into postcentral gyrus, parietal opercular cortex, supramarginal gyrus Insular cortex, extending into orbitofrontal cortex Left thalamus
Win anticipation – Loss anticipation	14 10	-6 58 12 -36 2 14	4.52 5.20	0.0870* 0.0991*	Frontal pole, extending into paracingulate gyrus Central opercular cortex, extending into insular cortex
Loss anticipation – Win anticipation	2168 1754 1218 208 137 100 1	-34 -60 40 -20 -2 52 -4 18 44 36 -76 30 -28 -82 26 34 -42 40 -48 14 50	5.45 5.57 5.94 3.81 3.58 4.30 3.35	0.002 0.003 0.001 0.037 0.043 0.038 0.049	Middle frontal gyrus, extending into superior frontal gyrus Precuneus cortex, extending into cuneal cortex Paracingulate gyrus Lateral occipital cortex (3) Supramarginal gyrus (2) Left caudate
Win outcome	58493 113 50 5 1 1	-34 -70 -28 8 -76 -38 -16 -56 -36 4 -12 -12 2 -18 -12 -50 -68 24	3.00 5.38 3.61 4.11 3.65 3.64	<0.001 0.026 0.043 0.046 0.049 0.050	Lateral occipital cortex, extending into inferior temporal gyrus Middle frontal gyrus Superior frontal gyrus, extending into paracingulate gyrus Temporooccipital cortex (1), supramarginal gyrus Brainstem
Loss outcome	34199 7355 2823 3	-52 -64 -28 52 8 -30 8 42 6 38 -16 40	3.40 4.06 5.28 4.74	<0.001 <0.001 <0.001 0.049	Frontal pole, insular cortex Superior parietal lobule Right thalamus Cingulate gyrus Left pallidum
Neutral outcome	23278 6166	-8 -74 -38 30 20 -12	3.47 5.94	<0.001 <0.001	Occipital fusiform gyrus, extending into temporal fusiform cortex Cingulate gyrus Orbitofrontal cortex, frontal pole
No win in win	19554 3649 3091 718 90 44 23 9	34 -34 -26 40 18 -6 -26 -28 32 -52 -46 8 26 -6 32 24 -30 0 -20 -30 -2 6 2 30	3.77 6.94 6.81 6.50 4.12 7.15 6.10 3.91	<0.001 <0.001 <0.001 0.002 0.04 0.015 0.034 0.047	Inferior temporal gyrus Precuneus cortex Left thalamus (6), left lateral ventricle Right thalamus (2) Parahippocampal gyrus, extending into temporal fusiform cortex Superior temporal gyrus, extending into middle temporal gyrus (5) Orbitofrontal cortex, Frontal pole

No loss in loss	43294	-8 -76 -38	3.12	<0.001	Frontal pole, insular cortex, right pallidum, right thalamus, right hippocampus, right putamen
Win – Neutral outcome	43760 402 269 244 14 5 4	-20 -86 -20 -54 -2 44 46 -38 4 54 -10 -10 56 -52 -10 -22 -84 46 60 6 -16	4.31 5.20 5.19 5.01 2.24 3.48 4.10	<0.001 0.021 0.024 0.021 0.042 0.049 0.048	Orbitofrontal cortex Left thalamus Inferior temporal gyrus Inferior frontal gyrus Precentral gyrus Postcentral gyrus Left hippocampus Insular cortex Cingulate gyrus (anterior division)
Loss – Neutral outcome	8430 4480 4270 2680 936 118 40	-20 -86 -20 -30 18 -18 0 22 20 28 16 -18 52 -26 -10 12 8 10 -10 6 6	4.84 5.50 5.78 5.59 6.62 6.17 5.16	<0.001 <0.001 <0.001 <0.001 <0.001 0.013 0.035	Right accumbens Superior frontal gyrus Cingulate gyrus (posterior division) Supramarginal gyrus, extending into angular gyrus Temporal occipital fusiform cortex Right caudate
Win – Loss outcome	31453 7348 369 16 6	4 -92 2 -2 32 -18 -20 30 46 -2 -72 44 26 -18 -12	4.48 4.23 5.16 2.67 3.32	<0.001 <0.001 0.015 0.049 0.048	Right accumbens Superior frontal gyrus Inferior temporal gyrus Frontal pole, precentral gyrus, extending into postcentral gyrus Insular cortex, right putamen
Loss – Win outcome	156 104 54 3	8 14 66 50 -26 -6 -32 20 -10 -42 22 -2	6.65 8.37 5.95 5.43	0.012 0.003 0.033 0.048	Frontal operculum cortex, extending into inferior frontal gyrus & OFC Insular cortex Orbitofrontal cortex
Win & no loss in loss	54088 1967 204 42 6 6 2	34 -52 -22 -8 64 12 -20 34 46 -26 38 12 -26 -14 -24 -4 -8 28 -48 -56 28	3.34 5.67 4.56 2.75 2.71 2.44 0.84	<0.001 0.005 0.030 0.049 0.049 0.050 0.050	Precuneus cortex Right accumbens Frontal pole Superior frontal gyrus Inferior temporal gyrus Right putamen Precentral gyrus
Loss & no win in win	25	-30 18 -8	7.03	0.025	Insular cortex, orbitofrontal cortex, superior frontal gyrus

*applying a corrected *p*-value yielded no statistically significant mean activation clusters for 'Win anticipation – Loss anticipation'-events; reported MNI coordinates refer to peak voxel locations after applying uncorrected *p*-value

APPENDIX B

Table B. Summary table of higher-level mean neural activation clusters across both groups for pre-specified regions of interest in response to task-related events (lower-level contrasts). Results were corrected for multiple comparisons by TFCE at FWE p=0.05.

Lower-level contrast	Cluster size (voxels)	MNI (x,y,z)	t-score	*p*-value	Structure
Win anticipation – baseline	1240	-10 24 26	1.0	<0.001	Anterior cingulate gyrus, left CC
	579	-20 8 0	1.0	<0.001	Left putamen
	405	-10 44 -8	1.0	0.011	Cingulate gyrus, medial PFC
	217	-14 -22 4	1.0	<0.001	Left thalamus
	150	20 12 6	1.0	0.008	Right cerebral WM, putamen
	90	-40 -2 12	1.0	<0.001	Central opercular cortex, insula
	62	30 24 8	1.0	0.004	Insula, frontal operculum cortex
Loss anticipation – baseline	1067	-8 26 24	1.0	<0.001	Anterior cingulate gyrus
	911	-18 8 -6	0.92	<0.001	Left putamen
	440	20 10 -4	0.79	<0.001	Right putamen
	289	-4 -26 -2	0.99	0.003	Left thalamus, brainstem
	167	32 26 0	0.80	<0.001	Insular cortex, OFC
	21	-38 -4 14	1.0	0.035	Left cerebral cortex
Win anticipation – Loss anticipation	315	6 48 10	0.96	0.044	Paracingulate cortex, right CC
	42	-28 -30 -14	0.96	0035	Left HPC, left CC/WM
	33	-36 2 12	0.97	0.035	Central opercular cortex, insula
Loss anticipation – Win anticipation	88	-10 6 4	0.95	0.055	Left cerebral WM, left caudate
	37	20 12 -6	0.92	0.078	Right putamen
	37	-30 24 2	0.97	0.038	Left insular cortex, left CC
Win outcome	4909	28 14 -20	1.0	<0.001	OFC, insular cortex
	1856	6 34 -6	1.0	<0.001	Anterior cingulate gyrus, right C
	441	28 -26 -10	1.0	<0.001	Right HPC
	391	-22 -28 -10	1.0	<0.001	Left HPC
	328	6 0 30	1.0	0.001	Anterior cingulate gyrus, right C
	16	-18 -6 26	0.95	0.047	Left CC/WM, left caudate, lat.V.
Loss outcome	1596	28 14 -20	1.0	<0.001	OFC, insular cortex
	1334	-42 22 -22	1.0	<0.001	Temporal pole, OFC, left CC
	838	10 42 6	1.0	<0.001	Anterior cingulate gyrus, right C
	812	10 8 -2	1.0	<0.001	Right caudate, right accumbens
	122	22 -28 -4	1.0	<0.001	Right thalamus, right WM
	60	-20 -30 -2	1.0	0.001	Left thalamus, left cerebral WM
Neutral outcome	790	30 18 0	0.0	<0.001	Right CC, insular cortex
	318	-34 18 -4	1.0	0.001	Insular cortex, left CC
	122	22 -30 -2	1.0	<0.001	Right thalamus, right CC
	58	-20 -30 0	1.0	0.002	Left thalamus, left cerebral WM
No win in win	890	30 18 -12	1.0	<0.001	Insular cortex, OFC, right CC
	271	-26 26 -6	1.0	0.002	OFC, left CC/WM
	54	24 -30 0	1.0	0.003	Right cerebral WM, thalamus
	22	-20 -30 -2	0.97	0.027	Left thalamus, left cerebral WM
No loss in loss	512	40 18 -6	1.0	<0.001	Insular cortex, OFC, right CC
	215	-36 18 -6	1.0	0.006	Insular cortex, OFC, left CC
	131	24 -30 -4	0.99	<0.001	Right cerebral white matter
	74	-20 -30 0	1.0	<0.001	Left thalamus, left cerebral WM
	52	-16 -4 26	1.0	0.003	Left cerebral WM, left caudate

Win – Neutral outcome	7392 4276	-34 24 -22 -4 32 -18	1.0 1.0	<0.001 <0.001	OFC, left CC/WM Medial frontal cortex, paracing.
Loss – Neutral outcome	2101 1587 1430 961 37	10 44 6 28 14 -20 -30 18 -20 10 10 4 4 -26 0	1.0 1.0 1.0 1.0 0.97	<0.001 <0.001 <0.001 0.001 0.031	Anterior cingulate gyrus, para,rC OFC, insular cortex OFC, left cerebral cortex/WM Right caudate, cerebral WM Right thalamus
Win – Loss outcome	1803 729 663 109 99	-4 32 -16 16 6 -16 -10 4 -14 -24 -34 -2 26 -32 -4	1.0 1.0 1.0 0.97 0.97	<0.001 <0.001 <0.001 0.033 0.030	Medial frontal cortex, subcall. C. OFC, right cerebral cortex Left CC, left accumbens Left cerebral WM, thalamusHPC Right HPC, cerebral WM, thal.
Loss – Win outcome	654 553	-30 20 -10 42 24 -2	1.0 1.0	0.001 0.005	OFC, insular cortex, left CC Frontal operculum, OFC, right C.
Win & no loss in loss	926 632 586 275 210 55 31	-10 4 -14 16 6 -14 -14 -34 6 26 -36 -4 30 -12 0 -16 -6 26 20 -4 24	1.0 1.0 0.99 0.97 0.99 0.95 0.98	<0.001 <0.001 0.011 0.031 0.015 0.048 0.022	Left cerebral cortex, accumbens OFC, right CC/WM, putamen Left thalamus, left cerebral WM Right HPC, right cerebral WM Right putamen (100%) Left lateral ventricle, caudate Right cerebral WM, caudate
Loss & no win in win	412 391	-30 18 -8 50 20 -2	1.0 0.98	<0.001 0.019	Insular cortex, OFC, left CC Inferior frontal gyrus, OFC, rCC

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