The motivational mechanisms driving the antidepressant effect of ketamine

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Declaration

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

Abstract

Ketamine is a rapidly-acting antidepressant and has shown to be effective in depressed individuals who have previously failed to benefit from other available treatments. An important question is how ketamine works. Addressing this might help inform more targeted and efficient treatments in the future. The aim of this thesis was to examine the neural, cognitive, and computational mechanisms underpinning the antidepressant response to ketamine in treatment-resistant depression. The work has specifically focused on motivational processing, since ketamine is particularly effective in alleviating symptoms of anhedonia, which are thought to be related to impaired reward-related function. Following a general introduction (Chapter 1), the first experimental chapter (Chapter 2) focuses on identifying suitable reward and punishment tasks for repeated testing in a clinical trial. Test-retest properties of various tasks are explored in healthy individuals, assessed by both traditional measures of task performance (e.g., accuracy) and computational parameters. Chapter 3 outlines a pilot simultaneous EEG-fMRI study in healthy individuals probing the neural dynamics of the motivation to exert cognitive effort, an important but understudied process in depression. The third study (Chapter 4) uses resting-state fMRI to examine how ketamine modulates fronto-striatal circuitry, which is known to drive motivational behaviour, in depressed and healthy individuals. The final experimental chapter (Chapter 5) examines which cognitive and computational measures of motivational processing (using tasks identified in Chapter 2) change following a single dose of ketamine compared to placebo in depression, using a crossover design. Based on preliminary findings, it is tentatively proposed that ketamine might affect reward processing by enhancing fronto-striatal circuitry functional connectivity, as well as by increasing exploratory behaviours, and possibly punishment learning rates. The general discussion (Chapter 6) discusses these findings in relation to contemporary models of anhedonia and antidepressant action, considering both the limitations of the work presented and possible future directions.

Impact statement

Depression is recognised as one of the most prevalent and debilitating conditions, affecting millions worldwide. Understanding how effective treatments of depression work, provides a direct translational link to making a future impact in psychiatry. In particular, the current thesis provides several important contributions related to our understanding of how ketamine works as an antidepressant, highlighting the value of cognitive, computational, and neural measures to psychiatry.

In Chapter 2 I show that several cognitive tasks assessing reward and punishment processes demonstrate sufficient reliability. This is an important methodological aspect that, thus far, has received limited consideration in the field. However, if cognitive neuroscience is to have an impact on translational ambitions in psychiatry, establishing the reliability of cognitive measures will be a key element for such successful efforts. These results thus provide encouraging evidence for both translational frameworks and research aiming to better understand individual differences in motivational processing.

Our understanding of cognitive effort is advanced in Chapter 3. Cognitive effort informs a variety of functions important in daily life, such as academic and work success. While this study did not directly examine real-life outcomes, it provides a cognitive and neural basis to examine this and how it might relate to depression, an underexplored area. Specifically, a more ecologically valid and more accessible task was developed (compared to previous paradigms), with results suggesting that motivation to exert cognitive effort is modulated by balancing rewards against the effort required to obtain them. Neuroimaging data suggested that effort sensitivity might be encoded in a network of prefrontal cortex regions and by a P3-like event-related potential. Future studies should explore whether these brain correlates of motivation are impaired in depression.

Chapters 4 and 5 attempt to clarify the motivational processes underlying ketamine's beneficial effects in depression. In line with models of anhedonia, we identified that ketamine increases

functional connectivity within fronto-striatal circuitry, with some of these changes linked to acute and sustained improvements in anhedonia. If replicated, this might indicate one possible neural mechanism of ketamine's beneficial effects. It was further observed that ketamine can increase exploratory behaviours, albeit this finding is preliminary due to the small sample size, and it is currently unclear whether this directly mediates ketamine's beneficial effects. This needs to be clarified in future studies. These findings nevertheless shed light on possible mechanisms of action of ketamine and open up new avenues to explore in depression.

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Finally, I would like to thank and dedicate this thesis to my family and particularly my husband, Lukas, who is equally deserving of a holiday after this PhD.

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List of abbreviations

AAS	Average artifact subtraction
ACC	Anterior cingulate cortex
AMI	Apathy Motivation Index
AMI-BA	Apathy Motivation Index - Behavioural Activation
AMI-ES	Apathy Motivation Index - Emotional Sensitivity
AMI-SM	Apathy Motivation Index - Social Motivation
ANOVA	Analysis of variance
BA	Behavioural activation
BCG	Ballistocardiogram
BDI-II	Beck Depression Inventory Second Edition
BMI	Body mass index
CADSS	Clinician-Administered Dissociative States Scale
CBT	Cognitive behavioural therapy
CEV	Constant expected value
CEVR	Constant expected value reversed
CRP	C-reactive protein
DAS-SF2	Dysfunctional Attitudes Scale Short Form 2
DEV	Decreasing expected value
dlPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEfRT	Effort Expenditure for Reward Task
EEG	Electroencephalography
EPI	Echo planar imaging
ERP	Event related potential
ESS	Effective sample size
ETPB	Experimental Therapeutics and Pathophysiology Branch
EV	Expected values
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FSS	Fatigue Severity Scale
FWE	Family-wise error
FWHM	Full-width at half maximum
GA	Gradient artifact
GSE	General self-efficacy scale
HC	Healthy control

ICA	Independent components analysis
ICC	Intraclass correlation coefficient
IEV	Increasing expected value
LOT-R	Life Orientation Test-Revised
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MID	Monetary incentive delay
MNI	Montreal Neurological Institute
MVC	Maximum voluntary contraction
NIMH	National Institute of Mental Health
NMDA-R	N-methyl-D-aspartate receptors
OFC	Orbitofrontal cortex
PCA	Principal components analysis
PCC	Posterior cingulate cortex
PCP	Phencyclidine
PEs	Prediction errors
PFC	Prefrontal cortex
PRT	Probabilistic reward task
RDoC	Research Domain Criteria
RL	Reinforcement learning
ROI	Region-of-interest
rsfMRI	Resting-state functional magnetic resonance imaging
RT	Response time
SHAPS	Snaith-Hamilton Pleasure Scale
SSRI	Selective serotonin reuptake inhibitors
STAI	State-Trait Anxiety Inventory
TE	Echo time
TEPS	Temporal Experience of Pleasure Scale
TR	Repetition time
TRD	Treatment-resistant depression
vlPFC	Ventrolateral prefrontal cortex
vmPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area
YMRS	Young Mania Rating Scale

List of Figures and Tables

Notes to examiners

Parts of Chapter 2 have previously been published in a pre-print:

Mkrtchian, A., Valton, V., & Roiser, J. P. (2021). Reliability of Decision-Making and Reinforcement Learning Computational Parameters.
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All findings from Chapter 4 have been published in a peer-reviewed article:

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The work reported in this thesis is entirely my own except for the contributions acknowledged below. My supervisor, Prof Jonathan Roiser, has contributed comments and guidance on all chapters of the thesis.

In Chapter 4, the functional magnetic resonance imaging (fMRI) data is a subset of a previously collected dataset from the Experimental Therapeutics and Pathophysiology Branch (ETPB) at the National Institute of Mental Health (NIMH), collected by a team of ETPB researchers and previously preprocessed and published by Dr Jennifer W. Evans, a staff scientist at ETPB:
Evans, J. W., Szczepanik, J., Brutsché, N., Park, L. T., Nugent, A. C., & Zarate, C. A., Jr (2018). Default Mode Connectivity in Major Depressive Disorder Measured Up to 10 Days After Ketamine Administration. *Biological psychiatry*, *84*(8), 582–590. https://doi.org/10.1016/j.biopsych.2018.01.027

The CRP inflammatory markers were collected by ETPB researchers and preprocessed by Dr Peixiong Yuan, a molecular biologist in the ETPB group.

In Chapter 5, a subset of the data (55%) was collected by Max Greenwald, Christina Wusinich, Claire Punturieri, Grace Anderson, and Kanique Thomas, all research assistants in the ETPB at the NIMH.

1 General Introduction

1.1 Major depressive disorder

Major depressive disorder (MDD) is one of the most common mental health conditions, affecting around 280 million people worldwide (Institute of Health Metrics and Evaluation, 2022). The current conceptualisation and diagnosis of MDD is based on reaching several symptom criteria. These are listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), one of the most widely used manuals for psychiatric diagnoses (American Psychiatric Association, 2013). They include the presence of an episode lasting at least two weeks with at least one out of two cardinal depressive symptoms: dysphoria ('low or depressed mood most of the day, nearly every day') or anhedonia ('markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day'). To meet a diagnosis of MDD, at least four (or three, if dysphoria and anhedonia are both present) of the following symptoms must additionally be present: weight change, sleep pattern change, psychomotor change, fatigue or loss of energy, feelings of worthlessness or guilt, indecisiveness or diminished ability to think/concentrate, and suicide-related thoughts/behaviours. All these symptoms, excluding weight change and suicidal ideation, should be present nearly every day. Thus, our current characterisation of MDD is based on a cluster of co-occurring symptoms, which must cause significant distress and functional impairment.

MDD is thus associated with large impairments in daily functioning, contributing significantly to the overall global burden of disease as the leading cause of disability (Wittchen et al., 2011). The need to effectively treat and prevent MDD is further highlighted by the associated increased mortality risk, most notably from suicide, which is the fourth leading cause of death in young adults (World Health Organization, 2021). Despite the devastating impact of MDD, mechanistic insight into its aetiology is lacking, hampering progress in predicting and treating MDD (Insel et al., 2010). In contrast to many other medical conditions, there are currently no approved objective diagnostic tools, such as a laboratory test, to diagnose or inform treatment options for MDD. There is a consensus amongst researchers that MDD is a complex psychiatric

disorder, thought to stem from multiple interacting risk factors including, genetic, environmental, and psychosocial (Fried & Robinaugh, 2020).

Indeed, research over the past several decades indicates that MDD is not a singular disorder but encompasses great heterogeneity between individuals. This is illustrated in part by the range and possible combinations of symptoms to obtain a diagnosis of MDD in the DSM-5. For example, in a study examining overlap among seven common depression scales, over 50 distinct depressive symptoms were reported, demonstrating low overlap in scales purportedly all measuring the same construct (Fried, 2017). This complexity has motivated calls for a paradigm shift in psychiatry research toward better understanding of specific symptom dimensions, which may map onto discrete neurobiological mechanisms more closely than categorical diagnoses. One example of this shift is the Research Domain Criteria (RDoC) by the NIMH (Insel et al., 2010). The motivation here is that such an approach is more likely to allow for the identification of mechanistic pathways underlying specific symptoms, as it is unlikely that a common mechanism will explain two individuals with completely different symptomatology, even though they might both be diagnosed with MDD.

1.2 Anhedonia

Historically, the focus in MDD has been on understanding and treating low mood; however, as will be discussed in the following sections, current MDD treatments do not adequately address symptoms of anhedonia. Although a cardinal symptom of MDD, anhedonia is also present in many other psychiatric disorders, such as schizophrenia, substance use disorder, and Parkinson's disease (American Psychiatric Association, 2013; Hatzigiakoumis et al., 2011; Loas et al., 2012). Aspects of anhedonia are also closely related to other symptoms, such as apathy, fatigue and avolition (Lambert et al., 2018; Pelizza & Ferrari, 2009) and it is thus considered a transdiagnostic construct (Husain & Roiser, 2018; Trøstheim et al., 2020).

Anhedonia is extremely clinically significant; it is associated with greater depression severity, loss of functioning, and suicidality (Ballard et al., 2017; Calabrese et al., 2014; Hall et al., 1999;

Moos & Cronkite, 1999; Spijker et al., 2001; Vinckier et al., 2017; Wichers et al., 2010; Winer et al., 2016). For example, in a large sample of over 900 patients with affective disorders, anhedonia was shown to be associated with suicide within one year (Fawcett et al., 1990). Similarly, a meta-analysis demonstrated that anhedonia is associated with suicidal ideation, even when controlling for general depression, suggesting that anhedonia may represent a critical risk factor for suicidal behaviours (Ducasse et al., 2018). A recent analysis of almost 4,000 MDD participants similarly identified that greater anhedonia was associated with greater persistent suicidal ideation (Bloomfield-Clagett et al., 2022). Interestingly, it has been suggested that self-reported loss of interest is more predictive of suicidal ideation than loss of pleasure (Winer et al., 2016), and similarly that loss of interest, on par with suicidal ideation, represents an acute suicide risk factor (Ballard et al., 2016). This indicates that symptoms of anhedonia might not be homogenous, as will be discussed in later sections, and that strong links exists between anhedonia and suicidal behaviours, highlighting the need to better understand this symptom.

The main hypothesis tested in this thesis is that ketamine's antidepressant effects, especially its anti-anhedonic properties, are driven by changes in neural, cognitive and computational processes relating to motivation. In the next section I will review common current treatments for MDD, namely psychotherapy such as cognitive behavioural therapy (CBT), and antidepressants such as selective serotonin reuptake inhibitors (SSRIs). I will argue that these treatments do not adequately address symptoms of anhedonia in MDD, highlighting the clinical importance of focusing on this symptom. I will then introduce the literature showing that ketamine can exert potent and rapid-acting antidepressant effects, even in those characterised as treatment-resistant depressed (TRD) patients. A particular focus will be to examine ketamine's anti-anhedonic effects, which may act independently of ketamine's general antidepressant effects. The two most common models of antidepressant mechanisms will then be reviewed. These aim to explain MDD and its treatment based on cellular mechanisms in the neuroplasticity model, while the cognitive neuropsychological model proposes explanations based on neural and cognitive mechanisms. It will be argued that, while these have been

informative for understanding treatment effects on mood, they are currently insufficient at providing explanations for anhedonia symptoms and lack sophisticated models for ketamine's beneficial effects. Instead, it will be argued, in line with current conceptualisations of anhedonia, that a number of reward and punishment processes, subserved by fronto-striatal circuits in the brain, might be relevant for understanding anhedonia, and by extension, ketamine's anti-anhedonic properties. I will synthesise the literature suggesting that impairments in reward learning, valuation and decision-making, and motivated effort are important in MDD and symptoms related to reward-processing. I will then review the literature examining ketamine's effects on neural and cognitive motivational processing. It is highlighted that this line of research is still at an early stage and thus only a handful of studies have focused on this, with the majority in experimental animals. I will conclude this chapter by outlining the thesis hypotheses and predictions, and explain how these will be tested across four experimental chapters.

1.3 Common MDD treatments are ineffective for anhedonia

Psychotherapy is delivered through talking therapy, with the most common type of treatment being CBT. The core tenets underlying CBT are based on Beck's cognitive theory of depression, which describes how individuals with depression have dysfunctional cognitive processing patterns in which they form negative views about themselves, the world, and the future (the 'cognitive triad') (Beck et al., 1979). This follows from the notion that an individual's cognition is based on attitudes and assumptions ('schemas'), which are expectations (or 'priors' in a Bayesian framework) derived from previous experience. Thus, the emphasis is on how individuals perceive events. CBT aims to correct these cognitive biases by identifying, challenging, and correcting dysfunctional beliefs (Beck et al., 1979).

CBT is an effective psychological intervention for MDD (Butler et al., 2006; Lepping et al., 2017), with about 60% of patients benefiting from it (Cuijpers et al., 2010; Rush et al., 2006). Despite this, CBT does not seem to adequately address symptoms of anhedonia (as measured with the Snaith-Hamilton Pleasure Scale: SHAPS) (Nord et al., 2019), while other symptoms such as low

mood and anxiety do improve. Although a recent study suggests that anhedonia can be improved with CBT, as measured with the anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire (Brown et al., 2021), this was not assessed in a randomised control study, and it is not clear how closely these two scales relate to each other.

In contrast to CBT, behavioural activation (BA) therapy, another form of psychotherapy, emphasises actions over cognition to reduce depressive symptoms (Kanter et al., 2010; Manos et al., 2010). The goal of BA is to increase engagement in behaviours that might result in rewards, through activity monitoring and scheduling, which over time become reinforced and thereby boost mood. This approach thus emphasises a relationship between the activities in which we engage and mood; whereas CBT stresses that low mood is primarily driven by dysfunctional thoughts. As BA targets components relevant to anhedonia (increasing rewarding activities), this treatment might be more beneficial for improving this symptom dimension. However, as of yet there is limited evidence to suggest this (Sandman & Craske, 2022). Network meta-analyses suggest that psychological treatments (including CBT and BA) are superior to waitlist controls, but there is little evidence for the effectiveness of one form over the other (Ciharova et al., 2021). Overall, however, very little research has examined different psychotherapy components and how they affect symptoms related to anhedonia; and although some recent efforts have been made to design psychotherapies specifically for anhedonia, these have not yet been examined in detail (Sandman & Craske, 2022; Winer et al., 2019). In addition, all psychological treatments require some degree of motivation and exertion of cognitive effort for effective treatment engagement, which might be particularly difficult for individuals struggling with motivation (Khazanov et al., 2021).

Antidepressant medication is the other major class of MDD treatments and tends to be the first type offered for depression, especially in moderate-to-severe cases (Bauer et al., 2007; Cleare et al., 2015). The antidepressant drugs used today are based on older compounds which were discovered serendipitously in the 1950s and later found to target the monoaminergic system (Hillhouse & Porter, 2015). This discovery allowed for newer drugs, with fewer side effects, to

be developed. However, since their discovery, antidepressants have not changed substantially in terms of their effects on the brain and still largely act to enhance monoamine neurotransmission. In particular, SSRIs were introduced in the second generation of antidepressants, as well as those primarily targeting noradrenaline, or a combination of both (Riggs & Gould, 2021). The advent of antidepressants led to the development of the monoamine hypothesis, which suggests that a deficiency in, e.g., serotonin, underlies MDD (Coppen, 1967). Although there is evidence to suggest that the monoaminergic and noradrenergic systems are involved in affective processes, and thereby indirectly in mood (Cowen & Browning, 2015; Ruhé et al., 2007), the monoamine hypothesis of depression does not adequately address the cause of depression as there has been little convincing evidence to suggest that depression is associated with reduced monoamine levels *per se* (Cowen & Browning, 2015; Hirschfeld, 2000).

Furthermore, almost 50% of patients do not benefit from current first-line antidepressant medications (Trivedi et al., 2006). Reward-related symptoms further seem particularly resistant to standard antidepressants. For example, across two large studies, the severity of an interest-activity dimension at baseline predicted lower remission rates with standard antidepressants (Uher et al., 2012). A similar pattern has been observed in adolescents (McMakin et al., 2012). There is also evidence to suggest that SSRIs may blunt neural responses to rewarding stimuli (McCabe et al., 2010), consistent with the observation that they can cause emotional blunting (Goodwin et al., 2017; Opbroek et al., 2002).

In summary, both psychological and pharmacological treatments inadequately address the core depressive symptom of anhedonia and instead might primarily target negative affect (Sandman & Craske, 2022). This is further evidenced by reward-related symptoms, such as anhedonia, being among the most prominent residual symptoms following both CBT and antidepressant treatment (Whiston et al., 2022). An additional important limitation of both treatment classes is that they take several weeks to impart clinical efficacy, and a sizable portion of patients respond only partially or not at all, exacerbating the global health burden of MDD. Despite the

prevalence and debilitating consequences of MDD, current treatments have not substantially changed in the past several decades, and these issues highlight the clear need for alternative and more effective treatment options.

1.4 Ketamine – a novel rapid-acting antidepressant

Over the past two decades, ketamine has emerged as a potentially potent antidepressant (Zarate & Machado-Vieira, 2017). In contrast to traditional pharmacotherapies, which primarily act through monoamine signalling, ketamine is a glutamatergic modulator, blocking N-methyl-D-aspartate receptors (NMDA-R). Importantly, and distinctly from standard treatments, ketamine has rapid-acting antidepressant effects. A derivative of phencyclidine (more commonly known as PCP), ketamine was originally developed in the 1960s and has been in use since the 1970s as anaesthetic agent (Domino et al., 1965). Outside the laboratory, ketamine became known as a 'club drug' due to its dissociative effects, especially during the 1990s rave scene (Jansen, 2000). Indeed, it was observed that ketamine also produces transient psychotomimetic and dissociative effects (Krystal, 1994). These observations led to ketamine being widely used in research to model symptoms of psychosis in healthy individuals since the 1990s.

Over two decades ago, against the backdrop of limited rodent studies suggesting that NMDA-R may be important in MDD and antidepressant response (Layer et al., 1995; Skolnick et al., 1996), a small proof-of-concept study in humans demonstrated that a single sub-anaesthetic dose (0.5mg/kg) of ketamine infused over 40 minutes can produce rapid-acting antidepressant effects (Berman et al., 2000). In seven patients with MDD, ketamine, but not placebo (saline solution), markedly improved mood, which lasted up to 2 weeks. Most notably, these effects persisted long past the acute pharmacological effects of ketamine, as the half-life of ketamine is relatively short, dissipating from the body within hours (Berman et al., 2000). This study was followed-up with a randomised, placebo-controlled, double-blind crossover trial of ketamine with 18 TRD patients (on average six previous failed antidepressant trials) (Zarate et al., 2006). As in the initial proof-of-concept study, TRD patients showed significant reductions in

depressive symptoms within two hours, lasting for one week, with the largest effect observed 24 hours post-infusion.

As mentioned, ketamine can produce several side effects. These mainly comprise transient dissociative and psychomimetic effects that resolve within the first hour or two (Acevedo-Diaz et al., 2020). Although some studies have reported that ketamine's antidepressant effects are associated with the dissociative side effects, suggesting that the dissociative effects are important for ketamine's antidepressant effects (Luckenbaugh et al., 2014; Niciu et al., 2018), others have only found a weak relationship (Ballard & Zarate, 2020; Mathai et al., 2020). Other studies, including pre-clinical work, have suggested that the antidepressant effect does not depend on the dissociative effects (Zanos et al., 2016). Although it is not yet clear what role ketamine's dissociative effects play in its antidepressant effects, and these do make the blinding of studies very challenging, importantly, the antidepressant effects consistently persist much longer than the initial dissociative symptoms.

Ketamine's rapid antidepressant effects have been replicated in numerous studies with TRD patients, including in active placebo randomised controlled trials (which control better for side-effects) (Murrough et al., 2013), bipolar patients without worsening mania symptoms (Diazgranados et al., 2010; Zarate et al., 2012) and in paediatric TRD (Dwyer et al., 2021). Indeed, several meta-analyses have shown the efficacy of ketamine in MDD (Coyle & Laws, 2015; Fond et al., 2014; Kishimoto et al., 2016; McGirr et al., 2015; Wilkinson et al., 2018), with an aggregated effect size (standardised mean difference) of 0.89 in reducing depressive symptoms 24 hours post-infusion (Kryst et al., 2020). Although ketamine does not produce an antidepressant effect in all TRD individuals, around 50-75% of patients show some level of clinical response (Krystal et al., 2019). An important finding, especially from a public health perspective, has been that ketamine further demonstrates potent anti-suicidal effects (Witt et al., 2020). In light of these studies, in 2019 a derivative of ketamine, esketamine, was approved by the U.S. Food and Drug Administration for the treatment of TRD, followed by the European Medicines Agency. This represents a significant advancement in treatment for MDD, which has

only seen a handful of new treatments approved in the last couple of decades, where almost all others have been based on a monoaminergic mechanism of action (Fasipe, 2019). Efficacy and safety concerns have, however, hampered wide adoption (Turner, 2019).

Intriguingly, recent studies show that ketamine also has rapid-acting anti-anhedonic effects. For example, in a randomised, placebo-controlled, double-blind crossover trial with 36 treatment-resistant bipolar depressed patients, ketamine rapidly improved symptoms of anhedonia compared with placebo, as measured with the SHAPS (Lally et al., 2014). This was most prominent one day following infusion but lasted up to two weeks. Interestingly, this improvement in anhedonia occurred even when controlling for general depressive symptoms, suggesting a specific impact on anhedonia. Similarly, in an open-label study with TRD patients, ketamine rapidly ameliorated anhedonia (Lally et al., 2015). An exploratory factor analysis on symptom scales, pooling across placebo-controlled trials of ketamine, showed that ketamine had the greatest effect on an 'amotivation' factor, among others (Ballard et al., 2018). Other studies have similarly shown that repeated doses of ketamine and esketamine can relieve symptoms of anhedonia in TRD patients (Delfino et al., 2021; Rodrigues et al., 2020; Wilkowska et al., 2021; Zheng et al., 2022), with one study suggesting that ketamine's anti-anhedonic effects partly mediated improvements in other symptoms, including low mood, suicidal ideation, and anxiety (Rodrigues et al., 2020).

This prior work suggests that ketamine has potent anti-anhedonic effects, with preliminary studies raising the possibility that the broader antidepressant effects of ketamine may be mediated through improvements in anhedonia (Lally et al., 2014). However, the precise neural, cognitive, and computational mechanisms underlying these changes remain unknown. This step is crucial to better understand ketamine's mechanisms of action and for the development of new therapeutic targets. Motivational processing provides a promising framework to examine the mechanisms underlying ketamine's anti-anhedonic effects, which may identify markers of successful treatment, and potentially inform the development of novel interventions that can alleviate symptoms of anhedonia.

1.5 Current models of antidepressant mechanisms

1.5.1 Neuroplasticity models

A central proposal of neuroplasticity models of antidepressant action is that they reverse dysfunctional synaptic plasticity mechanisms in MDD (i.e., the changing and shaping of neuronal connections in the brain) caused by chronic stress. In particular, disrupted homeostatic control of neural regions important for mood and cognition is thought to underlie MDD (Duman & Aghajanian, 2012; Kavalali & Monteggia, 2020). Homeostatic synaptic signalling here refers to the tendency of neural activity to maintain and revert to a certain "set point" of function in the face of perturbations. Thus, if a homeostatic process is impaired, it will be less robust to various perturbations, such as environmental stress. For example, there is evidence from animal studies to suggest that chronic stress can cause changes in glutamate transmission, intracellular signalling, functional connectivity, and synaptic loss in cortico-limbic circuitry (Duman & Aghajanian, 2012; McEwen et al., 2015; McEwen & Morrison, 2013). In support of this, chronic, but not acute, administration of common antidepressants has shown to enhance synaptic plasticity and reverse stress-induced impairments in rodents, promoting adaptive behavioural changes (Duman et al., 2021). Ketamine is thought to act through similar mechanisms, for example through increasing brain-derived neurotropic factor signalling, which promotes activity-dependent regulation of synaptic plasticity (formation of new synaptic connections); albeit on a different timescale and different specific mechanism than typical antidepressants (Duman et al., 2021). Ketamine's specific mechanism of action remains unclear however, with a number of possible cellular/molecular processes proposed to be implicated, including NMDAR-independent ones, disinhibition of glutamate release, and disinhibition of monoaminergic transmission (Riggs & Gould, 2021). The majority of studies examining ketamine's mechanism of action have focused on cellular mechanisms in preclinical models. However, it is not yet clear how these cellular mechanisms contribute to cognitive changes and the antidepressant effects of ketamine as observed in MDD patients.

1.5.2 Cognitive neuropsychological model

The cognitive neuropsychological model aims to provide a cognitive and neural mechanistic theory of the beneficial effects of common MDD treatments (Roiser et al., 2012; Warren et al., 2015). A central tenant of this theory rests on the proposition that common MDD treatments act on negative affective biases (i.e., a bias towards processing negative emotional information), which are commonly observed in depression and those vulnerable to depression (Roiser & Sahakian, 2013). Specifically, it proposes a hierarchical framework, such that susceptibility to negative affective biases occurs due to disruptions in limbic neural systems driven by changes in the monoaminergic projections innervating them, for example the amygdala, striatum, and prefrontal cortex (PFC). This represents a revision and extension of the standard monoamine theory of depression, suggesting that antidepressant drugs alter mood only indirectly, through the cumulative impact of changes in "bottom-up" negative biases (equivalent to negative perceptions), thereby also explaining why antidepressants take several weeks to work. These bottom-up negative biases may either cause depressive symptoms directly or also feed into "top-down" biases such as dysfunctional negative expectations (negative schemas, equivalent to priors in a Bayesian formulation), which themselves maintain negative bottom-up affective biases in a mutually reinforcing manner (Roiser et al., 2012). It has further been suggested that impaired 'cold cognition' (e.g., cognitive control) facilitates the contribution of bottom-up negative affective biases to top-down negative expectations. Importantly, CBT and common antidepressants are proposed to act at different levels within this hierarchy, such that CBT mainly affects top-down negative expectations (resolving these over time), while antidepressants act on bottom-up negative affective biases (potentially also facilitating the resolution of top-down biases) (Harmer, 2008; Roiser et al., 2012). Broadly consistent with this formulation, a recent meta-analysis synthesis found that CBT mainly affected prefrontal cortex (PFC) regions while antidepressants modified amygdala function (Nord et al., 2021).

As alluded to above, an important aspect of these models has been to explain the clinical observation that antidepressants, while having direct pharmacological actions, do not directly

affect mood, as it takes several weeks to observe clinical efficacy while direct pharmacological effects (e.g., blockade of the serotonin transporter) are evident after just a few days. It is proposed that the SSRIs instead directly influence affective biases, such that they elicit early changes in the basic processing of emotional information (Harmer & Cowen, 2013; Harmer et al., 2009). Importantly, however, interactions with the environment (especially the social environment) are required to recalibrate emotional associations, such that accumulated experiences of more positive affective biases lead, over time, to improvements in emotional priors and thereby mood; this also explains the consistent observation that combined treatment with both antidepressants and CBT is superior to either in isolation (DeRubeis et al., 2008). In support of this theory, several studies have shown that antidepressants can induce positive biases in MDD, both at the neural (e.g., reduced hyperactive amygdala response to negative stimuli) and behavioural level (e.g. boosting episodic memory for positive words), and interestingly that early changes in emotional processing are predictive of future antidepressant response (Browning et al., 2021; Browning et al., 2019; Ma, 2015).

Limited suggestions have been put forward to provide a cognitive model of ketamine's rapid-acting beneficial effects. For example, it has been suggested that ketamine might abolish previously acquired negative memory-associations, but not encoding of new associations (Stuart et al., 2015). Speculatively, ketamine might thus directly affect higher-order entrenched negative schemas, which would not require interactions with the social environmental to recalibrate (Godlewska & Harmer, 2021; Harmer et al., 2017). One suggestion is that this occurs by making these beliefs temporarily more plastic and thus amenable to change (Roiser et al., 2012). Overall, however, cognitive theories of ketamine's beneficial effects remain at a nascent stage and are limited by the small number of studies examining ketamine's cognitive effects in MDD.

1.5.3 Summary of antidepressant models

Neuroplasticity and cognitive models provide explanations of MDD and antidepressant action at different, complementary, levels of analysis, but as of yet their integration has been elusive

(Harmer et al., 2017). As a relatively new antidepressant, with a very different profile to existing agents, most studies on ketamine's beneficial effects have focused on its molecular and cellular mechanisms, and thus there is currently no prevailing cognitive model of ketamine's beneficial effects. Although the cellular level of analysis is important, it is noteworthy that drug development grounded in basic science has largely not succeeded in late-stage clinical trials (Riggs & Gould, 2021). This may occur, in part, because we do not have a good understanding of how the cognitive mechanisms underlying depression are linked to cellular changes. However, additionally an important limitation of the cognitive neuropsychological model is that it does not attempt to explain different mechanisms for different symptoms of MDD but instead primarily focuses on the low mood aspect of depression. Given the heterogeneity of MDD, and the importance of understanding anti-anhedonic effects as outlined above, a promising approach is to explore different processes related to reward and punishment processing to identify the precise neural, cognitive, and computational mechanisms of ketamine's anti-anhedonic effects (Cuthbert & Insel, 2013). This may in turn identify cognitive mechanisms driving treatment effects, allowing the development of markers of response, and potentially encourage the development of precision medicine in psychiatry.

1.6 A cognitive neuroscience perspective on anhedonia

In research settings, anhedonia is primarily measured with self-report questionnaires, such as the SHAPS, which was originally developed for assessment of clinical severity (Snaith et al., 1995). Although symptom scales like the SHAPS provided initial evidence of ketamine's anhedonic effects, it has increasingly been recognised that anhedonia is both cognitively and neurobiologically complex and cannot be mechanistically understood through symptom scales alone (Der-Avakian & Markou, 2012; Der-Avakian & Pizzagalli, 2018; Husain & Roiser, 2018; Treadway, 2016; Treadway & Zald, 2013).

Anhedonia was classically conceptualised as reflecting a deficit in consummatory processes, i.e., hedonic capacity, since individuals behave and report as if rewards are less rewarding. In fact, the term 'anhedonia' directly translates to 'without pleasure' (D'Haenen, 1996). However,

experimental studies examining this aspect have not found much support for a deficit in pleasure capacity (Amsterdam et al., 1987; Arrondo et al., 2015; Berlin et al., 1998; Clepce et al., 2010; Dichter et al., 2010; Swiecicki et al., 2009). For example, MDD patients do not report enjoying primary rewards, such as e.g., chocolate or sucrose, any less than healthy individuals during in-the-moment experimental assessments (Amsterdam et al., 1987). Similarly, patients with MDD rate non-food rewards, such as cartoons, as comparably funny to healthy individuals (Sherdell et al., 2012).

In contrast to these behavioural findings, the neuroimaging literature suggests that MDD patients show striatal hypoactivation to rewarding feedback, which has been interpreted as reflecting a deficit in consummatory processes by some (Borsini et al., 2020; Keren et al., 2018; Pizzagalli & Roberts, 2022). However, these studies have typically employed tasks in which the anticipation and delivery of rewards are difficult to dissociate. Usually, no behavioural differences between patients and healthy groups are observed in these studies either, complicating interpretations as decreased neural activity could signify impairment but also compensation or unrelated reward processing impairments (Kieslich et al., 2022). Moreover, the "reward" on these tasks is almost invariably in the form of secondary reinforcers, such as money. It is unclear whether 'consumption' of reward on these tasks, i.e., the receipt of money, can be equated to deriving pleasure from primary rewards, as it is not strictly possible to 'consume' secondary reinforcers in the same way. These studies may instead be measuring other aspects involved in reward and punishment processes, such as reward anticipation, valuation or learning. Furthermore, despite the aims of symptom scales, such as the SHAPS, to measure consummatory anhedonia, it is likely that such questionnaires probe several different processes, as they ask participants to rate past or future imagined rewards. Importantly, the degree of in-the-moment pleasurable experience cannot be measured directly using such scales.

The unidimensional view of anhedonia as reflecting purely diminished capacity to experience pleasure has therefore been challenged. Contemporary accounts additionally recognise

'anticipatory' and 'decisional' components (Gard et al., 2006; Klein, 1984; Treadway & Zald, 2011). Although several models of anhedonia have been proposed, these all emphasise the involvement of multiple reward and punishment processes, that depend on partially separable cognitive and neural operations, centred on dopaminergically innervated cortico-striatal circuitry (Admon & Pizzagalli, 2015; Bekhbat et al., 2022; Bishop & Gagne, 2018; Borsini et al., 2020; Cooper et al., 2018; Der-Avakian & Markou, 2012; Der-Avakian & Pizzagalli, 2018; Eshel & Roiser, 2010; Felger & Treadway, 2017; Husain & Roiser, 2018; Huys et al., 2021; Kieslich et al., 2022; Lucido et al., 2021; Pizzagalli, 2014; Rizvi et al., 2016; Rømer Thomsen et al., 2015; Treadway, 2016; Treadway et al., 2019; Treadway & Pizzagalli, 2014; Treadway & Zald, 2011, 2013; Wang et al., 2021; Zald & Treadway, 2017; Zhang et al., 2016). These roughly converge on relatively distinct cognitive processes such as learning, valuation and decision-making, and motivated effort. Related symptoms of MDD, such as lassitude and loss of energy, may also be related to reward and punishment processing. The following sections review these processes in MDD and anhedonia.

1.6.1 Learning

There has been a particular emphasis on understanding depressive symptoms as impairments in reinforcement learning (RL) processes. This lends itself to computational dissection and has thus been a core focus in computational psychiatry (Huys et al., 2021). Adaptive behaviour relies on learning which actions or stimuli maximise rewards and minimise punishments. This type of learning is thought to rely, at least in part, on phasic dopaminergic prediction errors (PEs) that signal the difference between expected and obtained outcomes (Schultz et al., 1997). Dopamine neurons in the ventral tegmental area (VTA) have been reported to correspond to such a signal, which is then transmitted to the striatum and the prefrontal cortex (PFC) to guide goal-directed behaviour (Frank & Claus, 2006; Pasupathy & Miller, 2005; Watabe-Uchida et al., 2017).

Both depression and anhedonia has been linked with lower striatal and behavioural reward PE signals (Admon et al., 2017; Chase et al., 2010; Chen et al., 2015; Gradin et al., 2011; Greenberg

et al., 2015; Halahakoon et al., 2020; Kumar et al., 2018; Kumar et al., 2008; Reinen et al., 2021; Robinson & Chase, 2017; Robinson et al., 2012; Vrieze et al., 2013). A common task in this context has been the probabilistic reward task (PRT), in which participants are presented with two perceptually similar stimuli (a long or short line) and asked to correctly identify them, with one stimulus being more frequently rewarded than the other (Pizzagalli et al., 2008; Pizzagalli et al., 2005). Healthy individuals develop a response bias toward the more frequently rewarded stimulus on this task (i.e., choosing this stimulus more often), while a lower reward response bias, regardless of perceptual accuracy, has been reported in several studies of anhedonia and depression (Huys et al., 2013; Pechtel et al., 2013; Pizzagalli et al., 2008; Pizzagalli et al., 2005; Vrieze et al., 2013). Individual differences on this task have further been associated with dopamine transporter availability in the ventral striatum, as well as fronto-striatal resting-state connectivity (Kaiser et al., 2018). Collectively, these studies suggest that anhedonia is associated with disrupted reward learning as a result of altered dopaminergic transmission.

Impaired behaviour on this task could however result from both diminished reward learning and/or reward sensitivity, which renders the specificity of anhedonia-related differences unclear. Huys et al. (2013) therefore re-analysed these data using a computational model and found that aberrant reward sensitivity (i.e., valuation), but not learning, was specifically associated with anhedonia and depression. It is not yet clear whether this effect reflects choice variability (i.e., more random responding) or diminished valuation *per se,* as these were not possible to dissociate between in the model. Similarly, Rutledge et al. (2017) found that neither moderate depression nor anhedonia was associated with dysfunctional reward PE encoding in a non-learning task. They suggested that previous results stemmed from aberrant downstream effects of PEs on learning. In line with this, lower connectivity between the VTA and striatum has been observed in MDD individuals during a reward-learning task (Kumar et al., 2018). This suggests that PE encoding in the VTA is not properly transmitted to the striatum, resulting in impaired reward learning. Similarly, Greenberg et al. (2015) reported a less marked relationship between striatal PEs and striatal activity during cues signalling rewards (which they termed "reward expectancy") in anhedonia, over and above other symptoms, but no blunting of striatal

activation corresponding to reward expectancy or PE *per se*. However, these neuroimaging studies used different tasks where no behavioural differences were observed and were not always analysed with computational models. Others have similarly found that learning signals are not lower overall in MDD, but specifically in medial orbitofrontal cortex (OFC), with lower ventral striatal PEs corresponding to greater anhedonia symptoms (Rothkirch et al., 2017).

A clearer approach to answering this question can be provided by examining RL using tasks in which learning and outcome valuation can be dissociated computationally (Chen et al., 2015). One suitable task to address this is a restless (reward and punishment outcome probabilities change slowly over time) four-armed bandit (Daw et al., 2006). However, no previous studies have examined how anhedonia correlates with this task. On a different RL task, anhedonia has been associated with lower reward learning rates (slower updating of reward values) as well as greater outcome sensitivity (Brown et al., 2021). Recent accounts suggest that the impairment may be specific to downstream PE signalling, but whether this is specific to anhedonia remains to be determined, and it is unclear if subtypes of anhedonia may still exhibit deficits in reward learning, putatively reflecting abnormal PE encoding (Cooper et al., 2018).

Beyond the examination of simple reward learning, other components of RL might be important in anhedonia. For example, many decisions in everyday life occur under uncertain conditions where values of different responses must be learned through exploration (Scholl & Klein-Flugge, 2018; Sutton & Barto, 2018). Under these circumstances, people are faced with a dilemma: whether to exploit (choose an action with a known outcome) or explore (choose an unknown or less-well-characterised option in the hope for an even better outcome). Goal-directed behaviours thus involve balancing exploitation of known outcomes with exploration of unknown, but possibly better options. Studies in this area emphasise that there are at least two types of exploration-based behaviours: random and directed (Wilson et al., 2014). Random exploration describes exploration by chance, resulting in behavioural variability, while directed exploration is a targeted information-seeking strategy to reduce the relative uncertainty of the expected value of action. Strategies to reduce the relative uncertainty of the expected value of

actions have been shown to drive goal-directed exploration (Badre et al., 2012; Frank et al., 2009).

This uncertainty-driven exploration has primary been associated with PFC function, with a specific focus on the rostrolateral PFC (rlPFC), and with genetic variants controlling dopaminergic function in the PFC (Badre et al., 2012; Frank et al., 2009; Zajkowski et al., 2017). Such goal-directed uncertainty-driven exploration can be examined in the clock task, in which participants are presented with a clock face and hand that rotates over five seconds (Moustafa et al., 2008). Stopping the hand at different times yields rewards of different amount and probability. Participants are asked to learn an optimal response time (fast or slow) to maximise rewards by sampling different time points. This task thus measures exploration based on response times, and has showed that lower uncertainty-driven exploration in schizophrenia is associated with anhedonia (Strauss et al., 2011) (although a recent study did not replicate the association with anhedonia in schizophrenia when using a different task) (Waltz et al., 2020). It has been highlighted that anhedonia might be associated with more stochastic responding across a number of studies, which would potentially correspond to random exploration (Robinson & Chase, 2017). However, this suggestion was based on studies quantifying exploration with a 'temperature' parameter, which can represent directed and random exploration, or low reward sensitivity (since reward sensitivity and temperature parameters trade off in RL algorithms), making it difficult to interpret (Robinson & Chase, 2017).

Despite theoretical accounts emphasising a potentially important role of goal-directed exploration in psychiatric disorders (Addicott et al., 2017; Huys et al., 2015; Scholl & Klein-Flugge, 2018), the general hypothesis that anhedonia is associated with reduced goal-directed behaviours has not been examined extensively in MDD. One previous study, using a different but conceptually similar task, suggested that depressed patients exhibited altered goal-directed exploration, such that they explored more when exploitation was the optimal strategy (Blanco et al., 2013). However, no study has yet examined whether uncertainty-driven exploration is lower in MDD or associated with greater anhedonia severity.

1.6.2 Valuation and decision-making

In order to make choices, organisms must represent the values of potential outcomes. Substantial research has implicated the PFC (e.g., ventromedial PFC - vmPFC, OFC, anterior cingulate cortex - ACC), striatum, and the anterior insula in such processes (Bartra et al., 2013; Rushworth et al., 2011; Tom et al., 2007). As discussed in the previous section, anhedonia might be associated with disrupted reward valuation, potentially reducing the difference in subjective values between options, which would make decisions more difficult. Interestingly, first-degree relatives of MDD patients with sub-clinical depressive symptoms showed a blunted reward bias, as assessed with the PRT which had been redesigned to remove the learning component (Liu et al., 2016). This effect was further associated with the degree of anhedonia reported, over and above general depressive symptoms, suggesting that low reward valuation might be a risk factor for MDD. A large amount of literature supports the observation that MDD patients show a lower reward bias on the PRT, which was confirmed in a recent meta-analysis where this impairment showed the largest effect size among various reward processing components in MDD (Halahakoon et al., 2020). Interestingly, reward bias in this task has shown to be sensitive to a novel drug for anhedonia (a kappa-opioid-receptor antagonist, which increases dopamine release in the ventral striatum) in a recent 'proof-of-mechanism' study (Krystal et al., 2020). However, computational analysis revealed that this was driven by reward learning, rather than reward sensitivity (Pizzagalli et al., 2020). Although, the specificity of the reward response bias remains debated, this measure might represent a potential mechanistic predictor of anhedonia treatment response and might therefore be particularly interesting in the context of a ketamine trial.

Valuation can also be examined through cost-benefit decision-making frameworks. A widely used paradigm is a gambling task examining subjective valuation of losses, gains and risks (Charpentier et al., 2017; Sokol-Hessner et al., 2009; Tversky & Kahneman, 1992). A common finding is that people tend to be both loss and risk averse, but few studies have investigated such processes specifically in anhedonia. However, aberrant loss and risk aversion have been

associated with suicidality and childhood trauma in depressed individuals, although the precise direction is mixed (Baek et al., 2017; Clark et al., 2011; Hadlaczky et al., 2018; Huh et al., 2016). While one recent study reported lower loss aversion with increasing negative symptoms in a non-clinical sample (Klaus et al., 2020), others have not found altered loss or risk valuation with depression (Chung et al., 2017; Zajkowski et al., 2017). Altered loss and risk aversion might therefore be more prominent with specific aspects of depression, such as suicidal behaviours. Although suicidality and anhedonia are closely linked, as discussed above, it is not yet clear whether loss and risk aversion are associated with anhedonia specifically as this has not been examined in detail previously.

Decision-making involving social information may also constitute an important distinct valuation process (Meyer-Lindenberg & Tost, 2012). Indeed, depression is marked by social impairments and poor social functioning (Kupferberg et al., 2016). This reduced interaction in social contexts could potentially further worsen depressive symptoms, as social isolation is known to be a risk factor for depression (Santini et al., 2020). There is however currently a dearth of studies in this area, and it is unclear how it might relate to anhedonia specifically, although social anhedonia might be an important component of depression (Barkus & Badcock, 2019).

1.6.3 Motivated effort

Obtaining rewards often requires willingness to exert effort. Animal and human studies suggest that effort processing recruits a network centred on the ACC, motor cortex and the striatum (Bonnelle et al., 2016; Chong et al., 2017; Croxson et al., 2009; Klein-Flügge et al., 2016; Kurniawan et al., 2013; Le Heron et al., 2018; Scholl & Klein-Flugge, 2018; Walton et al., 2006). Recent studies suggest that low motivation—observed in MDD, schizophrenia and several neurological disorders in particular Parkinson's disease—might stem from aberrant effort-based decision making mechanisms (Culbreth et al., 2018a; Husain & Roiser, 2018; Le Heron et al., 2018; Treadway & Zald, 2011, 2013; Zald & Treadway, 2017). It has been suggested that

dopamine might signal benefits over effort costs, while serotonin might specifically relate to sensitivity to effort costs (Pessiglione et al., 2018).

These processes can be investigated using effort-related decision-making paradigms. Individuals are typically asked to squeeze a hand dynamometer or quickly make multiple key presses to obtain rewards. For example, a common task used to assess motivation to exert effort is the Effort Expenditure for Reward Task (EEfRT), which assesses decision-making between an easy, low reward choice, or a hard effort task with varying reward levels and probabilities (Treadway et al., 2009). Greater anhedonia has been associated with lower willingness to expend effort (here button presses) for greater reward (Treadway et al., 2009; Treadway & Zald, 2011). Similar impairments in effort-based decision making have been observed in individuals with subsyndromal depression (Yang et al., 2014), which was correlated with anticipatory anhedonia. Similarly, lower effort expenditure for rewards has been observed in schizophrenia, with the reduction in motivation to exert effort correlating with negative symptoms or amotivation (Barch et al., 2014; Chang et al., 2019; Fervaha et al., 2013; Gold et al., 2013; Treadway et al., 2015). It should be noted that not all studies demonstrate a specific relationship between anhedonia and lower motivation (Cléry-Melin et al., 2011; Zou et al., 2020). Furthermore, across studies, the most consistent difference between patients and controls is lower willingness to exert effort for high reward and probability, rather than overall. This might result from impairments in constructing value representations or probability (Gold et al., 2013; Treadway et al., 2015). However, it is not yet clear whether the mechanisms underlying anhedonia in MDD and schizophrenia are similar (Culbreth et al., 2018a). Overall, these studies show a relatively consistent pattern of lower willingness to exert effort across psychiatric conditions associated with motivational symptoms.

Importantly, many previous effort-based tasks do not parametrically vary effort demands independently from rewards, making it difficult to determine which components might drive motivational impairments. In a parallel line of research, focused on apathy in neurological disorders, Bonnelle et al. (2015) developed an effort-related decision-making task, the Apple

Gathering Task, which aims to recreate ecologically relevant features of motivation. Decisions on this task are based on a single choice of either accepting or rejecting an offer, which may mimic real-life decisions more realistically for patients (Pessiglione et al., 2018). Importantly, in this task reward and effort levels are manipulated parametrically and independently. In healthy individuals, apathy positively correlates with effort sensitivity (rather than lower reward sensitivity) on this task (Bonnelle et al., 2016; Bonnelle et al., 2015; Chong, 2018). Interestingly, experimentally induced inflammation in healthy individuals causes increased effort sensitivity, but not reduced reward sensitivity (Draper et al., 2018), consistent with theories that propose that inflammation-based processes underlie anhedonia in MDD (Felger & Treadway, 2017).

To date, most studies have exclusively considered physical effort when assessing motivation in patient populations. However, successful functioning in society also requires motivation to exert cognitive effort. This has predominantly been examined in schizophrenia, where low cognitive motivation has been positively associated with negative symptoms (Chang et al., 2020; Culbreth et al., 2016; Culbreth et al., 2020). While studies using physical effort tasks suggest that impaired motivation might be due to impairments in reward components, cognitive effort tasks additionally suggest that individuals with schizophrenia show heightened sensitivity to cognitive effort costs. Few studies have examined cognitive effort in MDD. One previous study found that depressed individuals had lower willingness to exert cognitive effort compared with healthy controls (Hershenberg et al., 2016). Overall, however, it is unclear whether any motivational impairments in MDD are associated with diminished reward sensitivity or increased effort sensitivity or some combination of both. This will be important to delineate as the specific motivational impairment pattern could plausibly inform the specific treatment needed (e.g., impaired reward sensitivity may require a different treatment than excessive sensitivity to effort costs).

1.6.4 Summary

In summary, emerging research suggests that learning, valuation, and motivation are separate cognitive processes and rely on relatively distinct fronto-striatal neural mechanisms. Although

these processes have been separated into different categories, they all interact with each other to some degree. It is however unclear which aspects of processing are specifically related to anhedonia, with existing research suggesting that these processes are important in MDD and anhedonia, and that disruption in any could potentially drive symptoms (Husain & Roiser, 2018). As such, cognitive tasks offer the possibility of understanding the mechanisms driving both symptoms and treatment effects, especially when examined computationally. Employing different reward/punishment tasks in the context of a clinical trial is therefore a promising strategy to identify the mechanisms driving the anti-anhedonic effects of ketamine.

1.7 Ketamine and motivational processes

Very few studies have specifically examined how ketamine affects cognitive, computational, and neural reward and punishment processes, particularly in clinical samples. Preliminary studies did not provide evidence that a subanaesthetic dose of ketamine modulates performance on the EEfRT or on a simple reinforcement learning task, as examined in a randomised, double-blind, placebo-controlled, crossover clinical trial, albeit in a small sample of TRD patients (Lally, 2015; Mkrtchian et al., 2019; Wusinich et al., 2021). Examining similar processes in rodents, ketamine has been shown to acutely impair motivation to exert effort for rewards on the EEfRT (Griesius et al., 2020). Reinforcement learning on a probabilistic reversal learning task in rodents further seemed impaired under ketamine (Wilkinson et al., 2020). However, it is difficult to compare across these rodent and human studies, not least because rodents and humans may use different strategies during task performance. The dosages in the rodent studies were also much larger than the antidepressant dose in TRD patients, the ketamine impairments in rodents were typically observed at the highest ketamine dosage, and these effects were examined one hour post-ketamine. This instead suggests that these impairments are related to ketamine's sedative or dissociative effects, resulting in more general cognitive dysfunction, especially considering that ketamine also reduced food intake at the highest dose in the EEfRT (Griesius et al., 2020). Interestingly, a recent study in marmoset monkeys demonstrated a dose-related increase in reward response bias post-ketamine on an animal version of the PRT (Wooldridge et al., 2020).

Ketamine has been shown to modulate key brain regions involved in motivational behaviour. For example, increased glucose metabolism in the ACC, striatum and OFC has been associated with greater ketamine-induced anti-anhedonic response in TRD patients (Lally et al., 2014; Lally et al., 2015). In an open-label study, ketamine also normalised subgenual (sg) ACC hyper-activation to positive monetary incentives, which was associated with symptoms of anhedonia in MDD patients (Morris et al., 2020). In line with this, a study in marmoset monkeys showed that experimentally induced overactivation of sgACC led to blunted anticipatory arousal to rewarding cues, but not reward consumption. This neural and behavioural impairment was further ameliorated by a single sub-anaesthetic dose of ketamine, while an SSRI treatment did not have an effect (Alexander et al., 2019). As such, the ACC has been proposed to constitute a critical region in mediating the antidepressant effects of ketamine (Alexander et al., 2021). Ketamine also restored dysfunctional habenula function in rodents with depressive-like behaviours (Yang et al., 2018). This small region is known to modulate processes involved in punishment processing, particularly in conveying negative PEs (Matsumoto & Hikosaka, 2007), with disrupted habenula function shown in MDD patients and anhedonia (Lawson et al., 2017) and animal models of depression (Hu et al., 2020). The habenula has therefore been proposed as another important region for ketamine's anti-anhedonic effects, potentially having downstream influences on monoamines, especially dopamine (Cui et al., 2019; Gold & Kadriu, 2019; Pulcu et al., 2021).

In line with these studies, a meta-analysis found that acute sub-anaesthetic but not anaesthetic levels of ketamine administration were associated with greater dopamine levels in the cortex and striatum in rodents (Kokkinou et al., 2018). As dopamine is associated with many reward and punishment processes, it is possible that some of ketamine's anti-anhedonic effects stem from ketamine's downstream effect on dopaminergic systems (Rincón-Cortés & Grace, 2020). Altered basal ganglia glutamate has also been linked to anhedonia (Haroon et al., 2018; Haroon et al., 2016). Taken together, these studies raise the possibility that some of the beneficial

effects of ketamine are driven by changes in reward and punishment related processes. However, this has not been examined in detail previously in patients.

1.8 Thesis aims and Chapter summaries

The overall aim of the current thesis is to examine the cognitive, neural and computational mechanisms underpinning the antidepressant response to ketamine in TRD. Since ketamine is particularly effective in alleviating symptoms of anhedonia, this work will focus on several candidate cognitive processes involved in motivational processing, spanning learning, valuation/decision-making, and motivated effort, as well as the fronto-striatal circuitry thought to subserve these processes. These questions are addressed across four experimental chapters.

1.8.1 Chapter 2: Reliability of reward and punishment tasks

Chapter 2 examines the psychometric properties of several tasks examining different reward and punishment processes in healthy volunteers. Examining test-retest reliability and practice effects is an important prerequisite for testing ketamine's effects on motivational processes in a within-subjects design, such as a crossover clinical trial. Identifying tasks with acceptable psychometric properties allows for increasing the sensitivity of our subsequent ketamine trial (Chapter 5). Participants completed eight different tasks, twice across two weeks. These tasks included a modified version of the PRT, a restless four-armed bandit task, a clock task, a gambling task, a social decision-making task, a physical effort task, and two versions of a novel cognitive effort task. It was hypothesised that measures that have previously shown an association with symptoms, indicating sufficient variability is present, would show good reliability. It was further hypothesised that computational measures would show greater reliability than traditional model-agnostic ones.

1.8.2 Chapter 3: The spatiotemporal dynamics of motivation to exert cognitive effort: a simultaneous EEG-fMRI study

Impaired motivated physical effort has been consistently observed in anhedonia, yet the motivation to exert cognitive effort has not received similar attention and the neural

mechanisms underlying willingness to exert cognitive effort remain unclear. The aim of Chapter 3 was therefore to conduct a pilot study to examine the spatiotemporal dynamics of the motivation to exert cognitive effort, to optimise for use in a ketamine trial. To this end, one of the cognitive effort tasks from Chapter 2 was modified to provide a more ecologically valid version that can also dissociate reward from effort in driving motivational impairments. This task was used during simultaneous electroencephalography (EEG)-fMRI recording in healthy individuals. It was predicted that: 1) motivation to exert effort would increase with reward incentives and decrease with effort costs; 2) effort computations during the decision to accept would be positively associated with the N2 event-related potential (ERP) and ACC activation, while reward would positively scale with the P3 ERP, striatal and vmPFC activation; and 3) the neural generators of the N2 would be the ACC, and the P3 would be associated activation in striatum and vmPFC.

1.8.3 Chapter 4: The effect of ketamine on fronto-striatal circuitry in depressed and healthy individuals: A resting-state fMRI study

The main aim of Chapter 4 was to clarify the role of the fronto-striatal circuitry, which is known to drive motivational behaviours, in ketamine's effects in TRD. Ketamine has been shown to have opposite effects on motivational symptoms in MDD (improving reward-related symptoms) and healthy individuals (transiently causing mild symptoms of anhedonia). This was examined by re-analysing a previously conducted randomised, double-blind, placebo-controlled cross-over trial with a sub-anaesthetic dose of ketamine in both TRD and healthy individuals. All participants underwent resting-state fMRI scans two-days post-infusion. It was predicted that ketamine would increase fronto-striatal functional connectivity in depressed individuals but decrease it in healthy individuals. In addition, samples of inflammatory markers were examined, as decreased fronto-striatal connectivity has been associated with increased peripheral inflammation, motivating the secondary prediction that ketamine-induced fronto-striatal shifts would be associated with changes in ketamine-induced peripheral inflammation.

1.8.4 Chapter 5: The effect of ketamine on reward and punishment processing

Chapter 5 addresses the central hypothesis of the current thesis, that ketamine's beneficial effects in TRD are driven by changes in reward and punishment processing. This was tested in a randomised, double-blind, placebo-controlled, crossover clinical trial of ketamine in TRD patients. Reward and punishment tasks identified as having acceptable reliability from Chapter 2 were used, including the bandit, clock, physical effort and modified PRT tasks. Patients were tested at baseline and one day post-ketamine and placebo infusions. Additionally, healthy controls were tested at baseline. Three main predictions were tested: 1) that at baseline, compared with healthy individuals patients would show a lower reward response bias, as tested in the modified PRT, poorer reward learning and sensitivity in the bandit task, lower willingness to exert physical effort and overall lower exploratory behaviours as assessed in the clock task; 2) that these reward processing measures would correlate with anhedonic symptom severity in patients; and 3) that a single sub-anaesthetic dose of ketamine would increase these reward processing measures in TRD patients.

2 Reliability of reward and punishment tasks

2.1 Abstract

Cognitive tasks need to be assessed in terms of their psychometric properties if these measures are to become useful clinically and in the context of within-subjects designs. However, for many reward and punishment tasks reliability is unknown. To examine which reward and punishment tasks may be suitable to assess the mechanisms underlying ketamine's anti-anhedonic effects, test-retest reliability was evaluated in eight cognitive tasks that assess various aspects of reward and punishment processing. Tasks assessing learning and valuation included: a four-armed bandit task, measuring reward and punishment learning/sensitivity; an investor-trustee task, measuring social decision-making; a gambling task, measuring loss/risk aversion; a clock task measuring go/no-go learning and uncertainty-driven exploration; and a reward/punishment bias task (a variant of the PRT) measuring response bias. Computational parameters were derived from the four-armed bandit and gambling tasks, and the fidelity with which the models for these tasks could predict future behaviour at an individual level was assessed. Three novel paradigms measuring motivation to exert effort were also included. These differed in terms of either physical or cognitive effort; and the cognitive effort tasks further differed in valence. Healthy individuals (N=50) completed the task battery two weeks apart. Considerable variability in the reliability of measures was observed across tasks. The four-armed bandit and gambling task show promise for assessing reinforcement learning and decision-making in the context of within-subject designs, as both model-agnostic and computational measures showed fair-to-excellent reliability, and models could predict future behaviour. Similarly, the physical effort task shows potential with good-to-excellent reliability across measures. In contrast, the clock task may only be suitable to assess exploratory behaviours (good reliability), as no other measures were reliable. The cognitive effort tasks all had at least one measure of poor reliability and suffered from substantial ceiling effects, thus requiring further task adjustments. No measures were reliable in the investor-trustee task, suggesting that this task is unsuitable for within-subjects designs. Unfortunately, no measures could be analysed from the reward/punishment bias task due to an error in the task code that

was only discovered following data collection. The results of this chapter show mixed results both between and within eight reward and punishment tasks, highlighting the complexities of translating tasks for use in clinical contexts. Importantly, several tasks and measures showed acceptable reliability and were thus deemed useful for assessing the cognitive mechanisms underlying ketamine's antidepressant effects.

2.2 Introduction

Emerging research suggests that various aspects of reward and punishment processing might be important in driving MDD, specifically in symptoms such as anhedonia. These include processes such as learning, valuation, and motivation as discussed in Chapter 1 (Eshel & Roiser, 2010; Husain & Roiser, 2018). Disruption in any or all of these processes could presumably lead to symptoms of anhedonia and may therefore underpin some of ketamine's beneficial effects.

These cognitive processes can further be conceptualised in computational terms, which offer the advantage of examining behaviourally unobservable, but important, latent processes driving behaviour (Huys et al., 2016; Montague et al., 2004). The increasing adoption of computational approaches in cognitive neuroscience inspired the emerging discipline of computational psychiatry, which aims to better understand mental illness through computational methods, with the ultimate goal of transforming such knowledge into new personalised treatment strategies (Adams et al., 2016; Browning et al., 2020; Friston et al., 2017; Huys, 2018; Huys et al., 2016; Huys et al., 2011; Maia & Frank, 2011; Montague et al., 2012; Patzelt et al., 2018; Paulus et al., 2016; Paulus & Thompson, 2019; Teufel & Fletcher, 2016; Wang & Krystal, 2014; Wiecki et al., 2015). For a cognitive and computational approach towards understanding treatment response to be fruitful however, it is crucial that these measures capture individual characteristics reliably (Browning et al., 2020; Paulus et al., 2016).

Test-retest reliability is an essential prerequisite in both longitudinal (e.g., pre-post designs) and crossover study designs (e.g., when individuals receive both placebo and treatment) in which repeated testing occurs. The importance may be more vital in studies without the inclusion of a control arm, as any changes could simply arise due to repeated testing effects, such as learning or random effects, leading to false positives which would not be easily detected. Alternatively (or additionally), any treatment-induced improvements could potentially be obscured or attenuated by unreliable measurement, leading to false negatives. However, few prior studies have specifically investigated the test-retest properties of reward and punishment processing tasks. In terms of learning and valuation, reward response bias, using the PRT, has shown to

have adequate reliability (r=0.57) over a 40-day (mean) period, suggesting it may be appropriate for clinical use (Pizzagalli et al., 2005). However, two previous studies showed poor reliability of a simple RL task and an anticipatory reward task (Bland et al., 2016; Plichta et al., 2012). In contrast, several effort paradigms have shown adequate reliability, including in patients with schizophrenia (Ohmann et al., 2022; Reddy et al., 2015).

Computational analysis of behaviour has shown to improve reliability (Price et al., 2019). Few studies have however examined the reliability of parameters derived from computational models of reward and punishment tasks. In this context RL models have perhaps been the most influential in understanding how rewards and punishments influence behaviour. These parameters often include reward and punishment sensitivity (reflecting subjective valuation of the outcomes) and learning rates (reflecting how quickly individuals learn from better- or worse-than-expected outcomes), which have been associated with distinct symptomatology and neural signals (Daw & Doya, 2006; Huys et al., 2021; Niv, 2009). Parameters derived from a go/no-go RL task showed poor reliability in one study (Moutoussis et al., 2018), as did those from a two-step decision-making task assessing model-based versus model-free RL in another (Shahar et al., 2019). Interestingly, the reliability of parameters derived from the latter task was substantially improved through hierarchical estimation procedures (Brown et al., 2020)

Another set of models, prospect theory models, allow dissecting the cognitive processes driving economic decision-making (Kahneman & Tversky, 1979; Ruggeri et al., 2020; Schonberg et al., 2011; Sokol-Hessner & Rutledge, 2019; Tversky & Kahneman, 1992). These models propose that decisions under known risks can be driven by 1) risk aversion – the preference for certain over uncertain gains, and 2) loss aversion – weighting losses more heavily than gains. Risk and loss aversion vary across individuals, and these differences have been associated with psychiatric diagnoses and affective states (Baek et al., 2017; Charpentier et al., 2017; Charpentier, De Martino, et al., 2016; Charpentier, De Neve, et al., 2016; Chung et al., 2017; Hadlaczky et al., 2018; Hartley & Phelps, 2012; Klaus et al., 2020). Importantly, computational modelling has allowed researchers to dissociate risk and loss aversion and their contribution to symptoms

(Charpentier et al., 2017), and in particular risk aversion parameters have been reported to be fairly stable in both healthy and depressed individuals (Chung et al., 2017). Similarly, in another study parameters from a prospect theory model showed significant correlations over time (Glockner & Pachur, 2012; Scheibehenne & Pachur, 2015), although reliability was not assessed formally in these studies.

In general, reward/punishment tasks have not been extensively screened for reliability, using the gold-standard metric of intraclass correlation coefficients (ICCs), or practice effects. The aim of the current study was therefore to ascertain test-retest reliability and practice effects on several commonly used reward and punishment processing tasks. Eight different tasks were assessed twice in healthy individuals, two-weeks apart. Tasks included a four-armed bandit task, measuring reward and punishment learning; an investor-trustee task, measuring social decision-making; a gambling task, measuring loss/risk aversion; a clock task measuring go/no-go learning and uncertainty-driven exploration; a reward/punishment bias task (a variant of the PRT) measuring response bias, and three effort tasks differing in either physical or cognitive effort and the cognitive effort further differing in valence. These were selected based on representing different components of learning, valuation, and motivation, that either empirically or theoretically are linked to symptoms of anhedonia (see Chapter 1).

In addition to assessing reliability on model-agnostic measures derived from these tasks, RL and prospect theory model parameters were additionally computed for two of the tasks. The use of generative computational models provides the possibility of adopting a complementary perspective to understanding reliability, through the lens of prediction. Generative models offer a substantial advantage in that they can both explain and predict behaviour, unlike model-agnostic measures. Specifically, if they are reliable, computational parameters fit to one dataset should be able to predict future behaviour in the same individual. In other words, computational models can additionally be assessed by their ability to forecast future behaviour, equivalent to out-of-sample validation. This type of validation assesses model generalisability

and is often referred to as predictive accuracy (Busemeyer & Wang, 2000; Glockner & Pachur, 2012; Scheibehenne & Pachur, 2015), but it has rarely been used as a metric of reliability.

Thus, in the current study, standard measures of stability and reliability (respectively, practice effects and ICCs) were assessed on all model-agnostic and computational measures, and computational models were additionally assessed in terms of their out-of-sample predictive accuracy. Since most tasks have shown correlations with various symptom dimensions, suggesting they are sensitive to individual differences, it was hypothesised that most measures would exhibit at least adequate test-retest reliability, and that measures without a learning component would show low practice effects. In addition, it was hypothesised that computational parameters would show greater reliability than model-agnostic variables derived from the same tasks.

2.3 Methods

2.3.1 Participants

Fifty-four healthy participants were recruited from the UCL Institute of Cognitive Neuroscience Subject Database. Four participants were excluded for failing to complete the second session (final N=50: 32 females [64%]; age range=19-38; mean age=25.16, SD±5.48 years; mean education=17.38, SD=±3.24 years). Participants reported no current or past psychiatric or neurological disorder, cannabis use in the past 31 days, alcohol consumption in the past 24 hours, or any other recreational drug use in the week prior to participation. Participants provided written informed consent and were compensated at the end of their second session with a flat rate of £30 and a bonus of up to £20 based on task winnings. The study was approved by the UCL Psychology and Language Sciences Research Ethics Committee (Project ID Number: fMRI/2013/005).

Sample size was determined by an *a priori* power analysis in G*Power (Faul et al., 2007). The power analysis was based on the smallest effect size of interest, r=0.4, since reliability below this threshold is conventionally considered poor (Fleiss, 2011). Detecting an effect size of this magnitude, at the one-tailed 0.05 alpha level with 90% power, requires 47 participants.

2.3.2 Task battery and data analysis

Participants completed a battery of cognitive tasks measuring various aspects of reward and punishment over two sessions (mean test-retest interval = 13.96 days, SD=0.20). All tasks were presented on a laptop using MATLAB (R2015b, The MathWorks, Inc., Natick, MA, United States) with either Psychtoolbox (http://psychtoolbox.org) or Cogent (Wellcome Trust Centre for Neuroimaging and Institute of Cognitive Neuroscience, UCL, London, U.K.). To avoid potential fatigue effects, the tasks were administered in a pseudorandomised order such that no effort task was administered consecutively in the sequence. At the end of each session the computer randomly picked 100 trials across all the tasks to calculate the bonus won based on performance.

2.3.2.1 Four-armed bandit task

The restless four-armed bandit task assesses reward and punishment learning (Daw et al., 2006; Seymour et al., 2012). On each trial participants were asked to choose one out of four bandits (represented as boxes), which would display one out of four possible outcomes following a choice: reward (green token), punishment (red token), neither reward nor punishment (empty box) or both reward and punishment (red and green token; **Figure 2.1**). The probability of reward and punishment outcomes varied independently over time within each bandit (with a slow random walk), and independently between bandits. Participants were instructed on the non-stationary and independent nature of choice outcomes and were told that the goal was to maximize gains and minimize losses. The task lasted around 15 minutes with 200 trials in total.

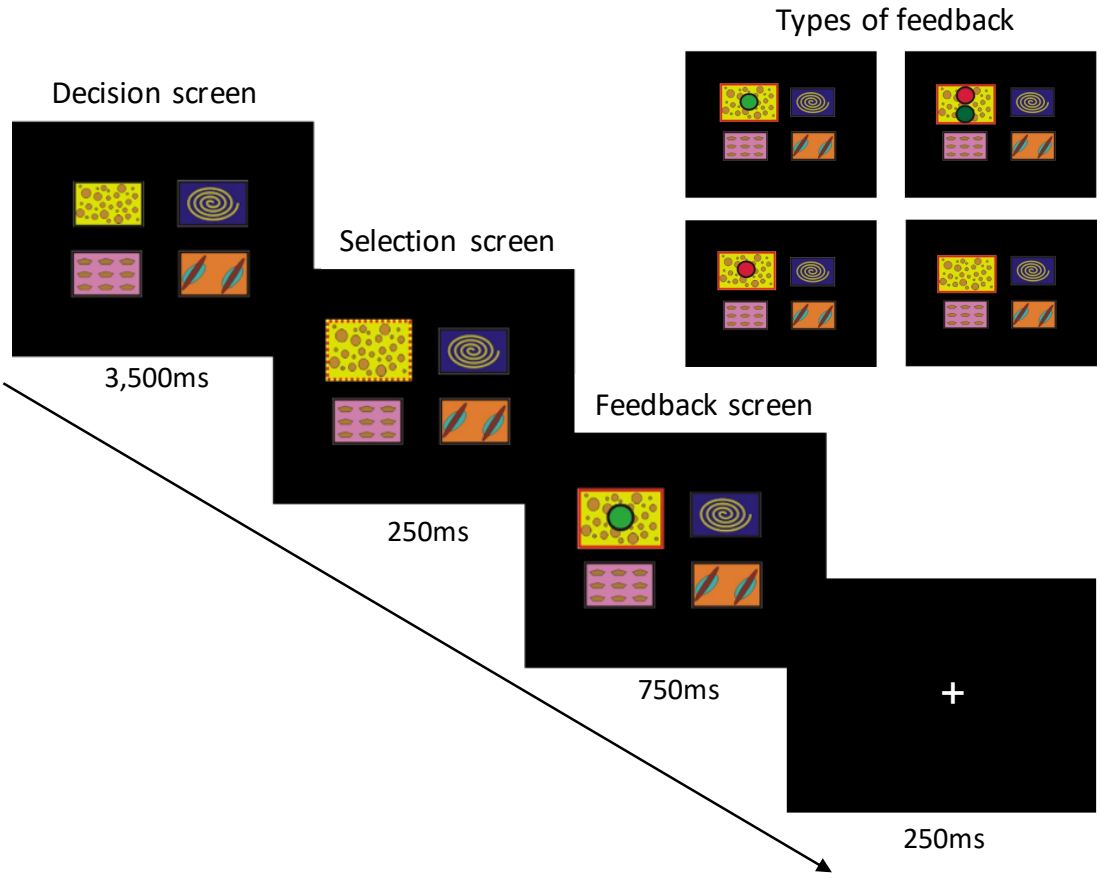

Figure 2.1 Example trial of the four-armed bandit task. On each trial, participants chose one out of four bandits and received one out of four possible outcomes: reward (green token), punishment (red token), neither reward nor punishment (empty box) or both reward and punishment (red and green token).

Model-agnostic measures were based on the probability of repeating a choice after win-only, loss-only and no outcomes (number of repeated choices/total choices in that category). A repeated-measures analysis of variance (ANOVA) was conducted with the within-subjects factors outcome (win, loss, neither) to assess whether the expected pattern of behaviour was observed. It was predicted that the probability of repeating a choice would increase after wins and decrease after losses (Daw et al., 2006).

Model-agnostic outcome measures for reliability analysis:

1. p(stay) after loss – p(stay) after neither
2. p(stay) after win – p(stay) after neither

2.3.2.2 Physical effort task

The physical effort task was adapted based on a combination of two previous tasks (Bonnelle et al., 2015; Treadway et al., 2009). In order to reduce the time and improve ease of administration, the number of reward and effort levels was reduced to three each, and the rate of repeated key presses required (instead of a hand dynamometer) was used to manipulate physical effort. On each trial, participants were presented with an offer indicating how much physical effort (20%, 50%, or 80%) they had to exert for a set amount of reward (3, 6, or 9 points; Figure 2.2). Participants were free to accept/reject offers based on their individual valuation of the effort-reward combination. Accepted offers were followed by the effort phase during which a bar was presented with a yellow horizontal line indicating the effort level (a higher line equated to a higher effort level). The effort phase involved participants pressing the spacebar with their non-dominant little finger at a rate fast enough to fill the bar above the yellow line, and maintain that speed for at least 10 consecutive seconds. A higher effort level thus involved pressing the space bar at a faster rate than a lower effort level. Each effort execution phase lasted for 15 seconds. To win rewards, the physical challenge had to be completed successfully. A failed or rejected trial resulted in 0 points. To avoid possible fatigue effects, 25% of accepted trials skipped the effort execution phase. No points were won on the

skipped trials and participants were informed that some accepted trials would be randomly skipped but this would not affect their final bonus.

Effort levels were individually calibrated during a practice phase where participants were asked to press the space bar as fast as they could for 15 seconds on four trials. The last two trials were considered for the effort calibration, which was based on the trial that had the fastest average key press response during a consecutive 10-second period. The task lasted for approximately 15-20 minutes and contained seven trials per effort x reward combination, resulting in 63 trials in total. Participants were instructed that the goal was to win as many points as possible.

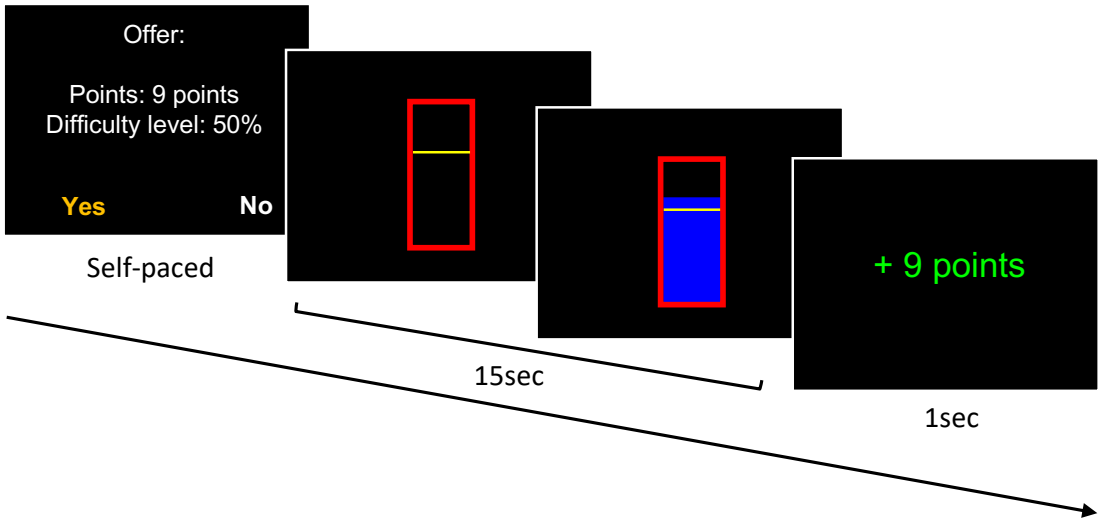

Figure 2.2 Example trial of the physical effort task. On each trial participants were free to accept or reject an offer based on the amount of reward available and the level of effort. The effort involved pressing the spacebar with their non-dominant little finger at a rate fast enough to fill the blue bar above the yellow line and maintain that speed for at least 10 consecutive seconds.

The physical effort task was introduced at a later stage of testing and thus the analysis only included 34 participants. Task validity was assessed by the probability to accept an offer, with reward (3, 6, 9 points), and effort (20, 50, 80%) as within-subject factors in a repeated-measures ANOVA. Linear contrasts of effort and reward were computed to assess the degree to which reward and effort influence behaviour. It was predicted that the probability to accept an offer would depend on both reward and effort level (Bonnelle et al., 2015).

Reliability outcome measures

1. Overall probability to accept: number of accepted trials/ total number of trials
2. Reward sensitivity: $\frac{1*p(accept\ at\ 9\ points)+0*p(accept\ at\ 6p)-1*p(accept\ at\ 3\ p)}{overall\ p(accept)}$
3. Effort sensitivity: $\frac{1*p(accept\ 80\%)+0*p(accept\ 50\%)-1*p(accept\ 20\%)}{overall\ p(accept)}$

2.3.2.3 Cognitive effort task (reward)

This task measures the motivation to exert cognitive effort to win rewards. The task structure was equivalent to the physical effort task but used a cognitive effort challenge (Figure 2.3). The cognitive effort consisted of correctly categorising ten consecutive numbers as odd or even within a time limit. Effort demands were manipulated by varying the time available to complete the cognitive challenge. If participants accepted an offer, they were presented with a number ranging from 0 to 9 and used the left/right key to indicate if the number was odd/even (0 was instructed to be even). If a correct response was given, the number turned green and a second number appeared until all ten numbers were completed. If an incorrect response was made, the number turned red, and the challenge was terminated. Participants only won points if they correctly completed all ten numbers within the time limit. Skipped, rejected, and failed effort execution trials resulted in 0 points.

The calibration involved completing 30 effort execution trials as fast and as accurately as possible. Effort levels (i.e., time to complete the effort challenge) were based on the fastest correctly executed trial, such that the 20%, 50%, and 80% effort levels corresponded to 180%, 150%, and 120% of the fastest correct calibration trial.

The task contained 72 trials in total (8 trials per effort/reward combination), resulting in a 20-minute task administration time. The odd/even response keys (left/right) were randomised across participants and sessions. Task performance and outcome variables for the reliability analysis were identical to the physical effort task.

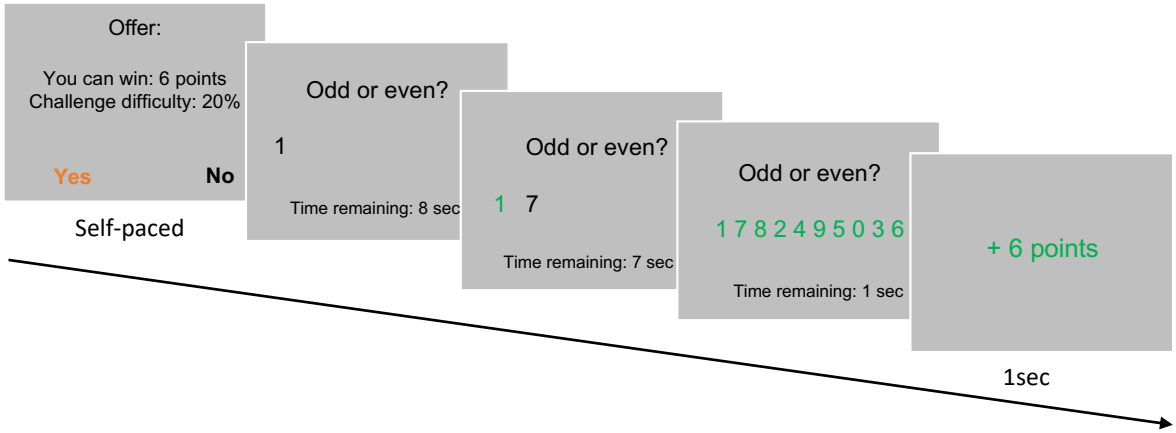

Figure 2.3 Example trial of the cognitive effort reward trial. On each trial participants were free to accept or reject an offer based on the amount of reward available and the level of effort. The effort involved categorising 10 numbers consecutively as odd or even under time pressure.

2.3.2.4 Cognitive effort task (punishment)

This task was included to measure motivation to exert cognitive effort to avoid negative outcomes. It was administered as a separate paradigm, but the task structure and effort challenge were identical to the cognitive effort reward task. During the offer phase participants were presented with the level of cognitive effort (20, 50, 80%) they had to exert to *avoid* losing points (-3, -6, -9 points; Figure 2.4). Participants were endowed with 100 points at the start of the task and told that the goal was to avoid losing points.

Due to the constraints of the task, rejection of an offer could not result in an outcome of zero points. In addition, the task structure had to be comparable to the cognitive effort to win rewards task to allow comparisons between the two tasks. For these reasons the task was designed such that rejected, skipped, or failed trials resulted in *losing* the points associated with that trial. The calibration procedure, number of trials, and task length were identical to the cognitive effort reward task.

One participant failed to complete this task and 3 outliers substantially skewed the distribution towards misleadingly high ICC values, resulting in 46 subjects for analysis. Task performance and reliability measures were identical to the other effort tasks.

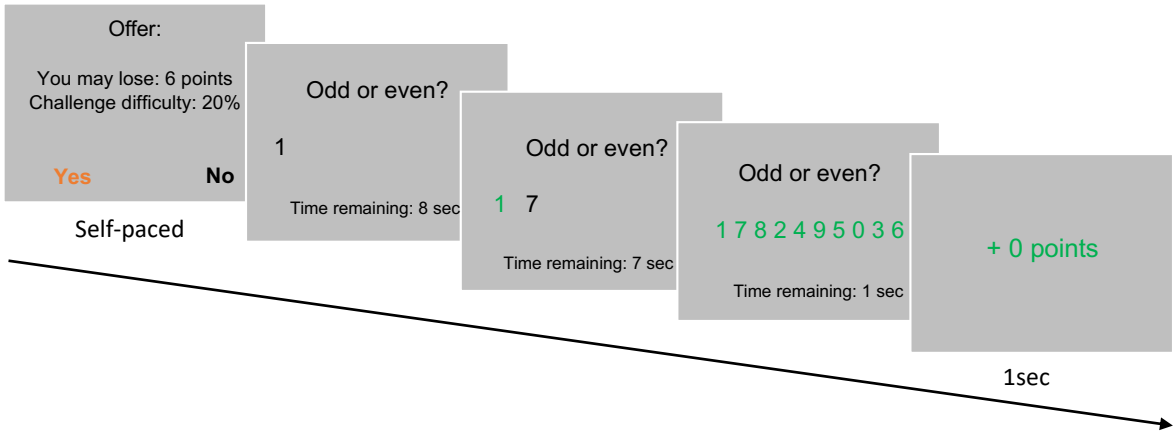

Figure 2.4 Example trial of the cognitive effort punishment trial. On each trial participants were free to accept or reject an offer based on the amount of points they could lose and the level of effort. The effort involved categorising 10 numbers consecutively as odd or even under time pressure.

2.3.2.5 Investor-trustee task

The investor-trustee task measures interpersonal decision-making in a social economic exchange game (Berg et al., 1995; King-Casas et al., 2008). Participants were allocated the role of the investor and told that they would play against another player (the computer), who embodied the role of the trustee. During the task, the investor was given the opportunity to invest up to 20 points to the trustee (Figure 2.5). From this investment, the trustee made a profit (3x investment amount) and returned the initial investment plus some of the profit to the investor. Thus, by investing points, the investor had the opportunity to make more points. The investor had the choice of investing a safe small amount or taking a larger risk and investing a larger proportion for potential greater profit. After each investment, participants could see how much the trustee made and how much of the profit was shared with the investor. The trustee shared some of the profit on all rounds except on round 10, during which the trustee defaulted (sharing none of the profit). This allowed assessing how sensitive participants are to the

experience of loss (i.e., how they invest on trial 11). There were 20 trials in total and the task was self-paced, lasting around 10 minutes.

The main outcome measure was the sensitivity to betrayal of trust (the difference between proportion invested in round 11 and mean proportion invested). The within-subjects factor of betrayal condition (mean proportion investment excluding trial 11, proportion invested in round 11) was used to assess this. It was predicted that the proportion invested on trial 11 would be lower compared to the mean investment.

Reliability outcome measures

1. Betrayal sensitivity: the difference between proportion invested in round 11 and mean proportion invested (excluding trial 11).

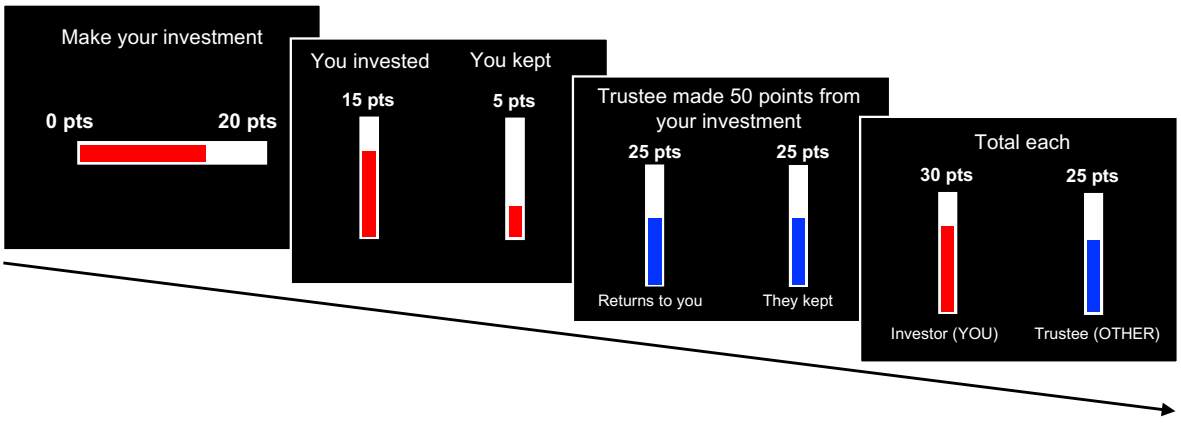

Figure 2.5 Example trial of the investor-trustee task. On each trial participants had the opportunity to invest up to 20 points to a trustee (computer) who made a profit and shared some of the profit with the investor.

2.3.2.6 Gambling task

The gambling task measures loss and risk aversion (Charpentier et al., 2017). On each trial, participants chose between a 50-50 gamble and a sure (guaranteed amount of points) option (Figure 2.6). The task was composed of two types of trials to disambiguate risk aversion from loss aversion. Loss aversion was measured using mixed-gamble trials, where the 50-50 gamble

contained a gain and a loss, and the sure option 0 points. Risk aversion was assessed with gain-only trials, such that the 50-50 gamble resulted in either a gain or nothing and the sure option was a guaranteed gain. Participants had 5000ms to make a choice and the chosen option was highlighted for 750ms. No outcomes were presented throughout the task.

An initial training phase was used to create individually-calibrated offers in a second phase. The training phase used a staircase procedure to calibrate individual indifference points of loss/risk aversion (50 loss and 40 risk aversion trials). The second block contained 120 trials (64 loss and 56 risk aversion) centred on the individualized risk/loss aversion indifference points, which were presented in random order. Participants were instructed that there were two blocks of the task but not that the first block was a calibration phase. The task lasted 15 minutes.

Calibration failed for one participant, resulting in data from 49 participants for this task. Model-agnostic measures were based on the probability to gamble on mixed and gain-only trials. It was predicted that gambling would be higher on mixed trials, which was assessed using a repeated-measures ANOVA with within-subjects factors gamble (mixed, gain-only).

Model-agnostic outcome measures for reliability analysis:

1. P(gamble) on mixed trials: number of gamble choices/total number of mixed trials
2. P(gamble) on gain-only trials: number of gamble choices/total number of gain-only trials

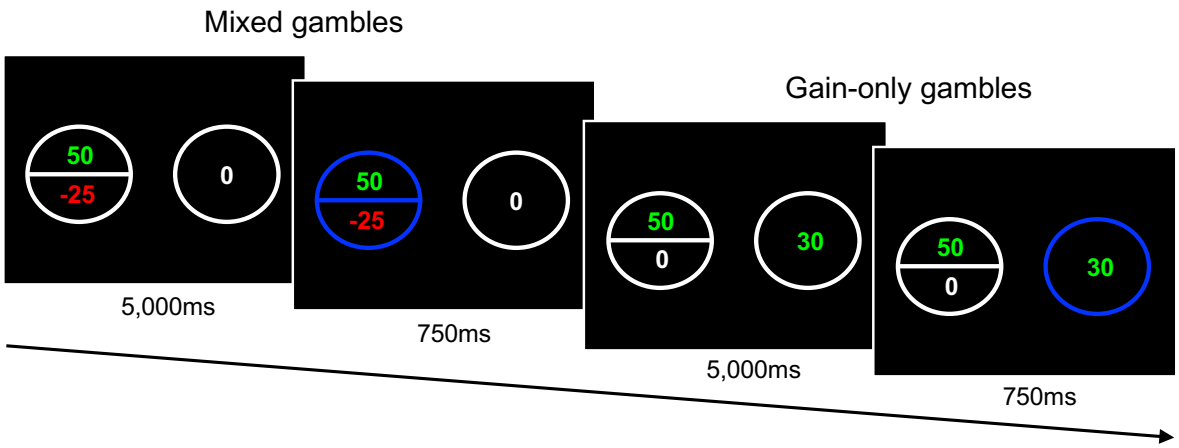

Figure 2.6 Example trials of the gambling task. On each trial, participants chose between a 50-50 gamble and a sure (guaranteed amount of points) option. Trials were either mixed gambles (50-50 chance of winning or losing points or sure option of 0 points) or gain-only trials (50-50 chance of winning or receiving nothing or sure gain). Mixed and gain-only trials were presented in an interleaved sequence.

2.3.2.7 Clock task

The clock task measures uncertainty-driven exploration and go/no-go learning (Frank et al., 2009). On each trial, a clock was presented with a rotating arm and participants were asked to stop it within a 5-second period (Figure 2.7). Depending on when they chose to stop it, participants could win different numbers of points. The task consisted of four conditions with different expected values (EV): 1) increasing expected value (IEV), promoting slower response times (RTs) to maximise reward; 2) decreasing expected value (DEV), promoting faster RTs to maximise reward; 3) constant expected value (CEV), reward probability decreased over time while reward magnitude increased over time (baseline condition); and 4) constant expected value-reversed (CEVR), the opposite of the CEV condition. There were four blocks in total, each corresponding to one of the task conditions. At the beginning of each block participants were told that they would interact with a new clock, for which they had to learn the optimal style of responding (e.g., fast or slow) to maximize rewards. There were 160 trials in total (40 trials/condition) with the task lasting approximately 17 minutes.

Performance was assessed by calculating go learning (mean RT difference between DEV and CEV) and no-go learning (mean RT difference between CEV and IEV). It was predicted that RTs

would be slower in the no-go compared with the go learning condition. A within-subjects ANOVA with factors learning (go, no-go) and session (1,2) was used. In the lack of a computational model to assess uncertainty-driven exploration (manifested behaviourally as RT swings), trial-to-trial variance was measured as an index of overall RT swings (Strauss et al., 2011):

$$\sqrt{\sum(RT(i) - RT(i+1))^2/(n-1)},$$

where i is trial number and n is the total number of trials. These trial-by-trial shifts in RT are thought to be related to changes in RPEs and that exploration occurs as a function of reward uncertainty (Frank et al., 2009).

Reliability outcome measures

1. Go learning: mean RT difference between DEV and CEV
2. No-go learning: mean RT difference between IEV and CEV
3. Overall RT swing

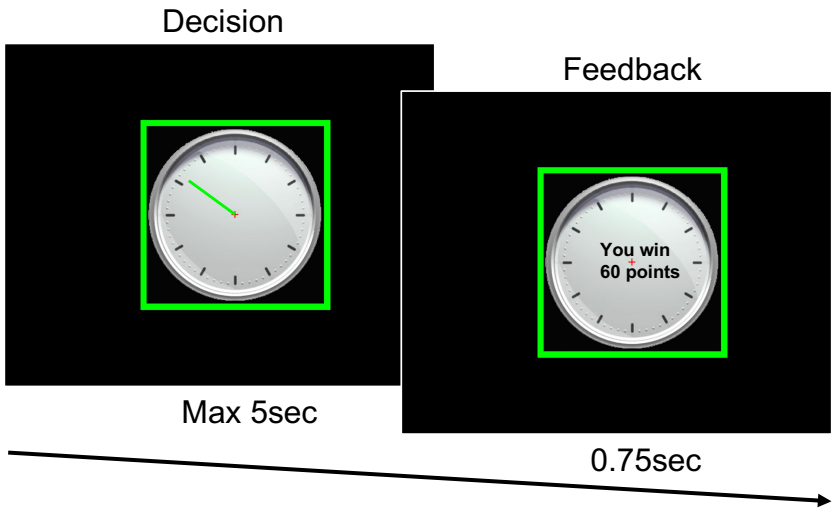

Figure 2.7 Example trial of the clock task. On each trial, participants were presented with a clock face on which the clock arm would rotate for five seconds, and participants had to learn the optimal style of responding (e.g., stop the arm early or late) to maximize rewards. The task consisted of four conditions with different expected values to promote different types of responding.

2.3.2.8 Reward/punishment bias task

This task was adapted from the PRT to measure reward and punishment response bias using a difficult visual discrimination paradigm (Pizzagalli et al., 2005). During the task participants were asked to indicate whether a presented line was short or long. Asymmetric reward and punishment reinforcement schedules were used to induce response biases for the more frequently rewarded/punished stimulus. Unfortunately, during analysis it was discovered that the response bias task had an error in the code, resulting in incorrect task conditions and thus no analyses were performed on this task.

2.3.2.9 General data analysis

Data were processed in Matlab (R2019b) and analysed in SPSS (v25, IBM Corp, Armonk, NY). Performance on all tasks was analysed with either repeated-measures ANOVAs or paired t-tests, with session (session 1, session 2) as an additional within-subjects factor to assess practice effects. For all analyses, $p<0.05$ (two-tailed) was considered statistically significant, and Huynh-Feldt corrected values were reported if sphericity assumptions were violated. Cohen's d_z effect sizes (within-subjects, using the standard deviation of the change score as the denominator) are reported for practice effects (Lakens, 2013).

2.3.2.10 Reliability analysis

Test-retest reliability was assessed with ICCs (ratios of intra-individual to inter-individual variability (Koo & Li, 2016; McGraw & Wong, 1996). ICC values vary between 0-1, where higher values indicate higher reliability and although negative values are theoretically possible, they are interpreted as a reliability of zero. A two-way mixed effects model ICC was used, as the time-interval between sessions was fixed. The ICC can be based on either single or average measures and the selection depends on how the task measures will be used in practice. For the purpose of the current study, we are not interested in the average value of an outcome measure across testing sessions, and therefore the ICC was based on single measures. Finally, an ICC can report absolute or relative reliability. Relative reliability, or "consistency", refers to the stability of the relative ranking of participants across multiple testing sessions. Thus, a high

consistency metric will occur if the relative ranking of participants' scores stays the same over time. By contrast, absolute reliability ("absolute agreement") additionally considers changes in individual mean scores between sessions and is therefore a more stringent criterion. Here we report consistency ICC measures as these can account for potential practice effects. The two-way mixed model for single measures and consistency agreement ICC is computed as (Koo & Li, 2016):

$$ICC = \frac{MS_B - MS_E}{MS_B + (k-1)MS_E}, (1)$$

where MS_B= mean square of between-subject variance, MS_E=mean square of the error variance, MS_W=mean square of the within-subject variance, *k*=number of testing sessions, *n*= number of subjects.

An ICC value below 0.40 was interpreted as poor, 0.4-0.6 as fair, 0.6-0.75 as good, and above 0.75 as excellent reliability, according to prior convention (Fleiss, 2011). Since outliers substantially influence ICC measures, scatter plots were drawn for all measures to detect possible outliers.

2.3.2.11 Computational modelling analyses

Computational models were fit to the four-armed bandit and gambling task. Modelling was performed with the hBayesDM package for R (v. 3.6.0; https://github.com/CCS-Lab/hBayesDM) (Ahn et al., 2017), which uses hierarchical Bayesian modelling in Stan (v.2.21.2). Hierarchical Bayesian modelling was achieved using Monte Carlo Markov chain (MCMC) sampling to estimate the posterior distribution of model parameter values. Hierarchical model-fitting uses group-level information to inform individual parameter estimates and has shown to provide more accurate parameter estimates than other model-fitting procedures (Ahn et al., 2011; Brown et al., 2020; Daw, 2011; Valton et al., 2020). Each model was fit using 4 chains with 1,000 burn-in samples and 4,000 samples per chain.

Several visual and objective diagnostics of the MCMC performance were conducted to examine convergence of the model-fitting procedure (Ahn et al., 2017; Kruschke, 2015). Each model was

inspected for divergences – none were found for any of the models. All subject- and group-level parameters were checked for a Gelman-Rubin statistic ($\hat{R}$) (Gelman & Rubin, 1992) value of less than 1.1 and an effective sample size (ESS) in the thousands. Trace plots of all subject- and group-level parameters were examined to ensure that the MCMC samples were well-mixed. If there were any issues with a model's MCMC performance, it was excluded as it would indicate that the model had not converged.

The models were fit for each session separately, using separate hierarchical priors (group-level parameters), as this has shown to provide more accurate fits (Valton et al., 2020), and we wished to avoid artificially inflating reliability estimates. We also estimated the winning model fits under a single hierarchical prior (session 1 and session 2 data together) as a sensitivity analysis. This estimation procedure was also used for sensitivity analyses of practice effects, as this approach is more conservative. Model comparison was performed with leave-one-out information criterion (LOOIC) where the winning model was the one with the lowest LOOIC. Several model validation checks were completed for the winning models (Daw, 2011; Kruschke, 2015; Wilson & Collins, 2019). To ensure that the winning model had identifiable parameters, we examined pair plots of the posterior distributions of the group-level parameters to determine that no major trade-off was occurring between parameters. We also examined if the winning model had recoverable parameters by generating simulated data for each participant based on their parameter estimates.

2.3.2.12 Posterior predictive performance

To assess to what extent an individual's future behaviour can be predicted using a generative model fit to their own task performance two weeks earlier, we calculated the probability of participants' choices on each trial (i.e., the softmax output – see below), given their session 2 data and model parameter estimates from session 1. Probabilities were averaged across trials for each individual. Since hierarchical parameter estimation produces 'shrinkage', effectively pulling parameter estimates from different individuals closer to each other (which improves estimation accuracy), it is possible that future performance may also be predicted above-

chance using other participants' parameter estimates from session 1 (e.g., participant A's parameter estimates from session 1 predicting participant B's session 2 choices). We therefore assessed whether using an individual's model parameter estimates from session 1 predicted the same individual's choices on session 2 better than using all other subjects' model parameter estimates. To construct the latter measure, for each subject, we predicted trial-by-trial choices on session 2 based on parameter estimates from every other participant's session 1 model, and averaged the probabilities across all participants.

2.3.2.13 Four-armed bandit task: Computational modelling

The bandit task data were fit with seven different models from the hBayesDM package, following the exact specifications from Aylward et al. (2019) (Table 2.1). The parameters from the winning model were used for reliability assessment.

Model	Parameters					
bandit4arm_lapse_decay	Rew sensitivity	Pun sensitivity	Rew LR	Pun LR	Lapse	Decay
Bandit4arm_lapse	Rew sensitivity	Pun sensitivity	Rew LR	Pun LR	Lapse	
Bandit4arm_4par	Rew sensitivity	Pun sensitivity	Rew LR	Pun LR		
Bandit4arm_2par_lapse			Rew LR	Pun LR	Lapse	
Bandit4arm_singleA_lapse	Rew sensitivity	Pun sensitivity	LR		Lapse	
Igt_pvl_decay	Decay rate	Shape	Consistency	Loss aversion		
Igt_pvl_delta	Learning rate	Shape	Consistency	Loss aversion		

Table 2.1 Computational models fitted to the four-armed bandit task. Models and nomenclature are from the hBayesDM package. Rew: Reward; Pun: Punishment; LR: Learning Rate.

The main family of models of interest were the reinforcement learning models (*bandit4arm*). The *Bandit4arm_4par* model was calculated by the following equations (Aylward et al., 2019):

$$Value_{t(i)}^{rew} = Value_{t(i)}^{rew} + Reward\ Learning\ Rate \times Prediction\ Error_{t(i)}^{rew} \quad (2)$$

$$Value_{t(i)}^{pun} = Value_{t(i)}^{pun} + Punishment\ Learning\ Rate \times Prediction\ Error_{t(i)}^{pun} \quad (3)$$

'Rew' and 'pun' refers to the reward (1,0) and punishment (0,-1) values on each trial (t) for a given bandit (i).

$$if\ i = chosen\text{: } Prediction\ Error_{t(i)}^{rew} = Reward\ Sensitivity\ \times\ Reward\ Outcome(t) - Value_{t-1(i)}^{rew}\ (4)$$

$$if\ i = unchosen\text{: } Prediction\ Error_{t(i)}^{rew} = -Value_{t-1(i)}^{rew}$$

$$if\ i = chosen\text{: } Prediction\ Error_{t(i)}^{pun} = Punishment\ Sensitivity\ \times\ Punishment\ Outcome(t) - Value_{t-1(i)}^{pun}\ (5)$$

$$if\ i = unchosen\text{: } Prediction\ Error_{t(i)}^{pun} = -Value_{t-1(i)}^{pun}$$

The subjective reward and punishment values were passed through a softmax function to estimate the probability of choosing a given bandit on each trial (j represents all bandits):

$$Choice\ Probability = \frac{\exp\left(Value_{t(i)}^{rew} + Value_{t(i)}^{pun}\right)}{\sum_j \exp\left(Value_{t(i)}^{rew} + Value_{t(i)}^{pun}\right)}\ (6)$$

The *Bandit4arm_2par_lapse* model excluded the sensitivity parameters in Eq. 4 and 5, and the *Bandit4arm_singleA_lapse* model had a single learning rate that did not vary separately for rewards and punishments Eq. 2 and 3). The choice probability (Eq. 6) additionally included terms with a lapse parameter (irreducible noise) in the *bandit4arm_lapse* and *bandit4arm_lapse_decay* model:

$$Choice\ Probability = \frac{\exp\left(Value_{t(i)}^{rew} + Value_{t(i)}^{pun}\right)}{\sum_j \exp\left(Value_{t(i)}^{rew} + Value_{t(i)}^{pun}\right)} \times (1 - Lapse) + \frac{Lapse}{4}\ (7)$$

The *bandit4arm_lapse_decay* model also included a decay parameter (information about bandits not recently chosen were gradually forgotten about):

$$if\ i = unchosen: Value(i) = (1 - Decay)\ \times Value_{t-1(i)}\ (8)$$

The *Igt_pvl_decay* and *Igt_pvl_delta* models are described in Aylward et al. (2019) and are prospect valence learning models including parts of prospect theory and reinforcement learning.

2.3.2.14 Gambling task: Computational modelling

Three prospect theory models were fit to the gambling task (Ahn et al., 2017; Charpentier et al., 2017; Kahneman & Tversky, 1979; Sokol-Hessner et al., 2009) (Table 2.2). Modelling was conducted on the second phase of the gambling task (i.e., on individually calibrated trials). Parameters from the best fitting model were used for the reliability assessment.

Model	Parameters		
Ra_prospect	Risk aversion	Loss aversion	Inverse temperature
Ra_noLA	Risk aversion		Inverse temperature
Ra_noRA		Loss aversion	Inverse temperature

Table 2.2 Computational models fitted to gambling task. Models and nomenclature are from the hBayesDM package.

The full prospect theory model, *ra_prospect*, was estimated with the following equations:

$$EV(gamble) = 0.5\ \times\ gain(t)^{Risk\ aversion} + 0.5\ \times\ Loss\ aversion\ \times\ -loss(t)^{Risk\ aversion}\ (9)$$

$$EV(sure) = sure(t)^{Risk\ aversion}\ (10)$$

On each trial (t) the subjective expected value (EV) of the gamble and sure option was calculated. These subjective expected values were passed through a softmax function to calculate the estimated probability of choosing the gamble option:

$$p(gamble) = \frac{1}{1 + \exp\left(-Inverse\ temperature\ \times\ [EV(gamble) - EV(sure)]\right)}\ (11)$$

For the *RA_noLA* model, the loss aversion parameter was omitted and the risk aversion parameter was omitted from the *Ra_noRA* model.

2.3.2.15 Exploratory analyses

Demographic correlations. Pearson's correlations were used to explore associations between age, years of education, and task performance for all tasks in the first session. Independent t-tests were used to explore associations between gender and task-performance (model-agnostic and computational parameter measures). All p-values were Bonferroni-adjusted for the number of tests conducted (25 task variables * 3 demographic variables=75 tests, Bonferroni-adjusted alpha-level: 0.05/75=0.0007). To contextualise any non-significant effects here, a sensitivity power analysis suggests that with a sample size of 50 participants, we would have 80% power to detect significant correlations of at least 0.37 at an uncorrected alpha level (0.05) and 80% to detect correlations of 0.54 at a Bonferroni-corrected alpha level (0.0007).

Effort tasks. The effort tasks were substantially modified from previous studies to adapt for clinical use. Effort success rates were therefore analysed as a manipulation check, using a repeated-measures ANOVA with effort levels (20, 50, 80%) and session (1,2) as within-subjects factors. As these tasks have similar designs, we also explored how they related to each other on all common outcome measures across session.

2.4 Results

2.4.1 Four-armed bandit task

2.4.1.1 Model-agnostic results

As expected, there was a main effect of outcome type on behaviour ($F_{(2,98)}$=117.39, p<0.001, η_p^2=0.71; Figure 2.8a). The probability to repeat a choice was significantly greater after wins compared with both losses and outcomes on which neither wins nor losses occurred, and greater after neither compared with losses (all p<0.001). There was no significant main effect of testing session ($F_{(1, 49)}$=0.01, p=0.91, η_p^2<0.001), but there was a significant outcome-by-session interaction ($F_{(2,98)}$=3.12, p=0.049, η_p^2=0.06), reflecting slightly increased repeated choices after wins and decreased repeated choices after losses on session 2. However, the difference in the tendency to repeat a choice between session 1 and session 2 did not reach significance following any of the outcome types (loss: $t_{(49)}$=1.45, p=0.15, d_z=0.21; win: $t_{(49)}$=0.87, p=0.39, d_z=0.12; neither: $t_{(49)}$=0.54, p=0.59, d_z=0.08), and therefore we do not interpret this result further. The model-agnostic outcome measures of the bandit task exhibited good reliability (Figure 2.8b).

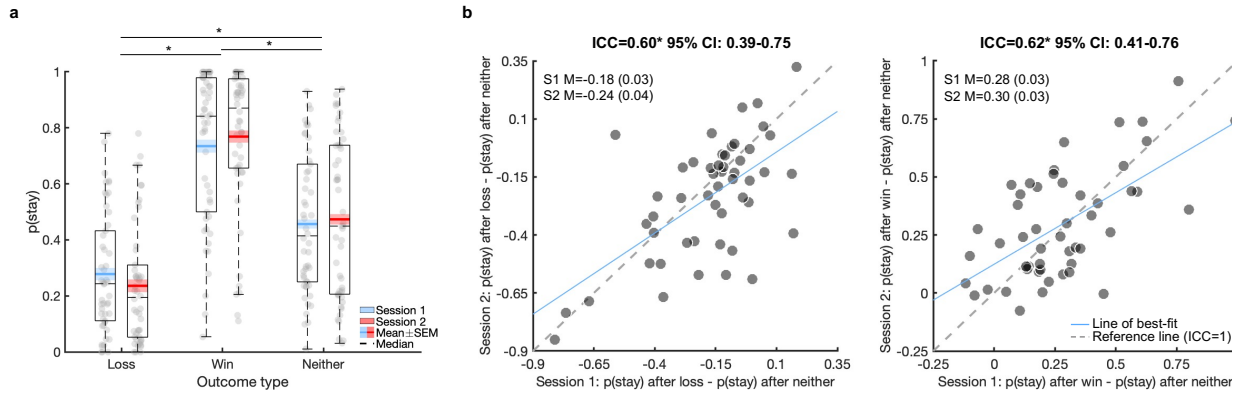

Figure 2.8 Basic behaviour, practice effects, and test-retest reliability of model-agnostic measures on the four-armed bandit task. Boxplots of the four-armed bandit task showing probability to stay after a certain outcome in session 1 and 2 (a). The probability to stay was significantly different after each outcome type (Loss<Neither<Win) but no clear practice effect was evident. Scatter plots and reliability of the four-armed bandit task model-agnostic measures comparing behaviour on two testing sessions approximately 2 weeks apart (b). Consistency (assesses relative ranking over time) intraclass correlation coefficients (ICC) are presented. S1: Session 1; S2: Session 2; M: Mean. Numbers in brackets represent standard error of the mean. *p<0.001

2.4.1.2 Computational model

Model comparison indicated that the winning (most parsimonious) model was the five-parameter *Bandit4arm_lapse* model (Table 2.3), consistent with previous reports (Aylward et al., 2019). Although the *bandit4arm_lapse_decay* model has previously shown to best fit the four-armed bandit task (Aylward et al., 2019), this model exhibited a number of Gelman−Rubin statistics $\hat{R}$ values greater than 1.1 and ESS <100. The ESS remained <100 for a number of parameters and trace plots showed poor mixing even when the sample size per chain was increased to 10,000 and default argument settings changed to: adapt_delta=0.99, stepsize=0.5, max_treedepth=20 (suggested parameter settings by hBayesDM defaults if model does not converge) (Ahn et al., 2017). This indicates signs of poor convergence, and the *bandit4arm_lapse_decay* model was therefore discarded.

Model	S1: LOOIC	S2: LOOIC
Bandit4arm_lapse	**21419.77**	**20469.63**
Bandit4arm_4par	21426.74	20513.87
Bandit4arm_singleA_lapse	21663.92	20667.74
Igt_pvl_decay	21834.23	21060.78
Igt_pvl_delta	22392.60	21294.36
Bandit4arm_2par_lapse	25523.77	25421.07
bandit4arm_lapse_decay*	-	-

Table 2.3 Model fits for the four-armed bandit task from the hBayesDM package. The winning model has the lowest Leave-One-Out Information Criterion (LOOIC) and noted in bold here. S1: session 1; S2: session2. *This model exhibited poor convergence and was excluded.

Three individuals were excluded due to difficulties in obtaining mean parameter estimates, as multiple peaks were evident in the posterior distribution of at least one parameter. The *Bandit4arm_lapse model* was therefore re-fit without these participants. Excluding these participants did not affect test-retest reliability inference. All parameters other than the lapse parameter showed high recoverability (Figure 2.9a), and synthetic data from the winning model accurately recapitulated real data (Figure 2.9b).

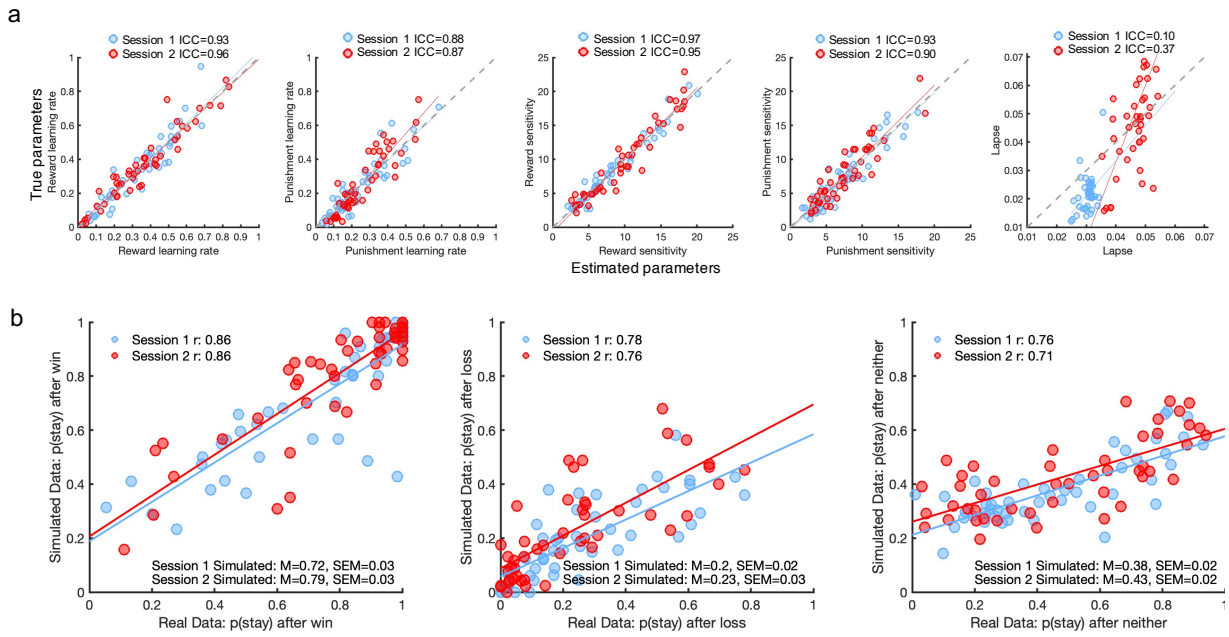

Figure 2.9 Model checks of the winning model from the four-armed bandit task. Plots show parameter recovery (a) and simulated against real participant data (b). Intraclass correlations (ICCs) represent two-way mixed model for single measures and absolute agreement. P(stay): probability to stay; M: mean; SEM: standard error of the mean; r: Pearson's correlations.

Examining practice effects on model parameters, there was a significant increase in the reward sensitivity ($t_{(46)}$=3.00, p=0.004, d_z=0.44) and lapse parameters ($t_{(46)}$=8.88, p<0.001, d_z=1.29) on session 2, but not on any of the other parameters (reward learning rate: $t_{(46)}$=1.28, p=0.21, d_z=0.19; punishment learning rate: $t_{(46)}$=1.74, p=0.09, d_z=0.25; punishment sensitivity: $t_{(46)}$=1.28, p=0.21, d_z=0.19; Figure 2.10a). However, there were no significant practice effects when the data were fit under a single hierarchical prior, which is more conservative (all p>0.06; reward learning rate d_z=0.14, punishment learning rate: d_z=0.20; reward sensitivity d_z=0.27; punishment sensitivity: d_z=0.08; lapse: d_z=0.04). All estimated Bandit4arm_lapse model parameters, except the lapse parameter, demonstrated fair-to-good reliability (Figure 2.10b), which did not substantially change when parameters were estimated under a single hierarchical prior (any ICCs that changed decreased by maximum 0.01).

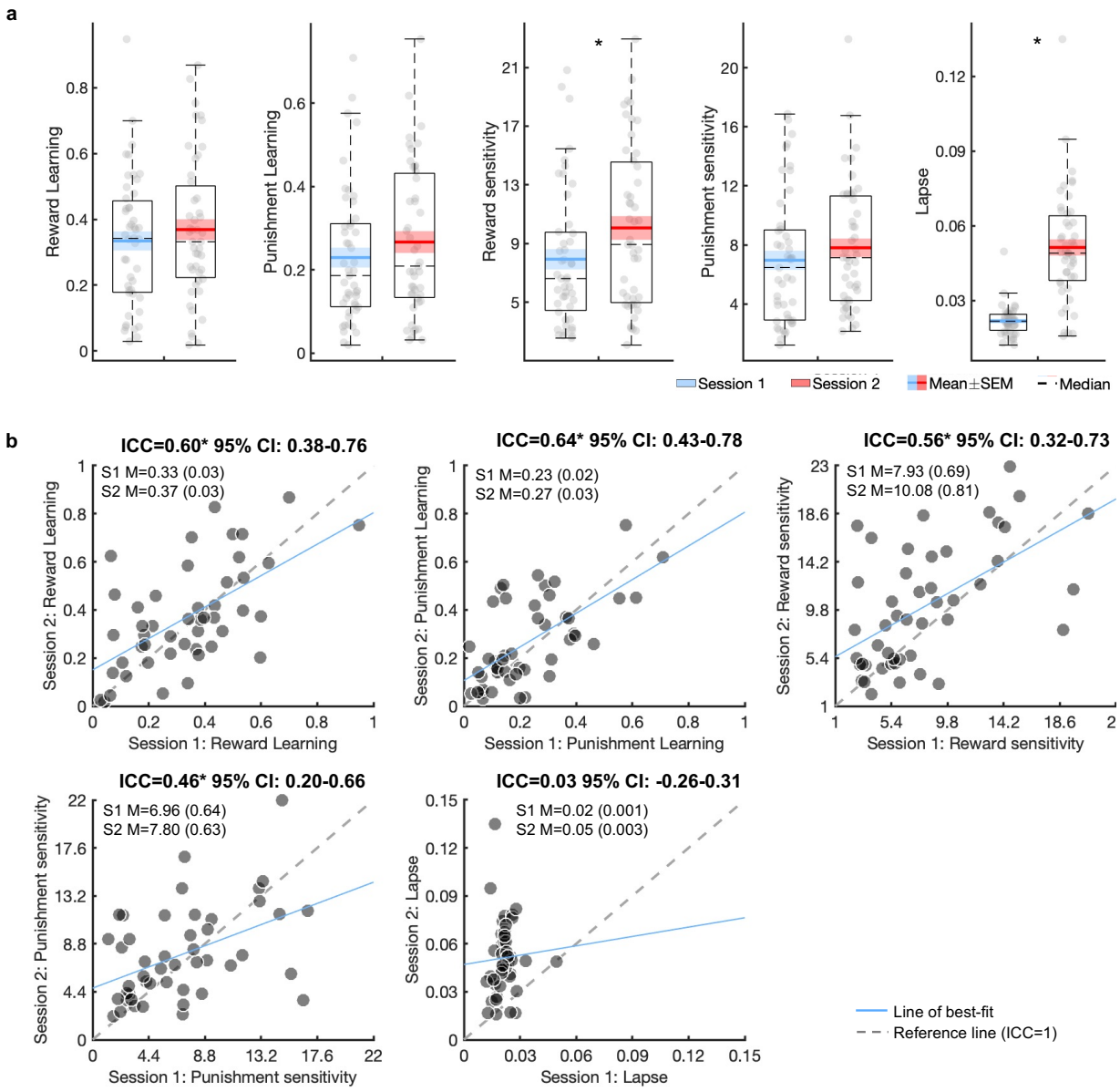

Figure 2.10. Practice effects and test-retest reliability of the winning reinforcement learning model parameters derived from the four-armed bandit task. Boxplots show point estimates of the Bandit4arm_lapse model parameters in session 1 and 2, fit under separate priors (a). Scatter plots and reliability of the Bandit4arm_lapse model parameters over session 1 and 2 are presented (b). Consistency (assesses relative ranking score over time) intraclass correlation coefficients (ICC) are presented. SEM: standard error of the mean; CI: confidence interval; S1: Session 1; S2: Session 2; M: Mean. Numbers in brackets represent standard error of the mean. *p<0.05.

Examining the future posterior predictive performance of the winning model revealed that parameter estimates from session 1 predicted task performance on session 2 substantially better than chance (mean=42%, chance=25% accuracy; $t_{(46)}$=9.10, p<0.001; Figure 2.11a),

indicating that the model could predict future choices by using a generative model fit to the same participants' data two weeks earlier. Using an individual's parameter estimates to predict their own future choices was significantly better than when that prediction was based on the average of the other participants' session 1 estimates ($t_{(46)}$=3.20, p=0.003; Figure 2.11b), signifying good individual-level model generalizability.

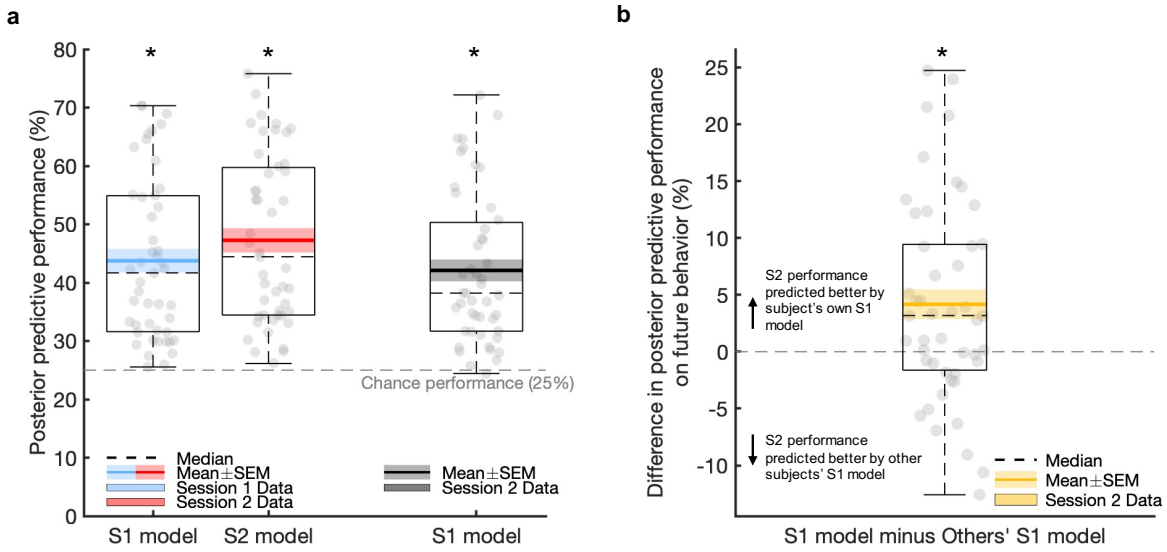

Figure 2.11 Posterior predictive performance of the winning reinforcement learning model derived from the four-armed bandit task. Boxplots depicting accuracy of bandit4arm_lapse model in predicting choices (a). Model estimates from session 1 (S1) predicted future session 2 (S2) behaviour above chance (black boxplot). Both S1 and S2 model estimates also predicted behaviour on the same session significantly above chance (blue and red boxplots). Predicting future performance (session 2 data) using a participant's own model parameter estimates was significantly better than using other participants' S1 model parameter estimates (b – zero indicates mean accuracy from other participants' parameter estimates). SEM: standard error of the mean. *p<0.01.

2.4.2 Physical effort task

Acceptance rates depended on both reward and effort (interaction: $F_{(1.963,64.783)}$=8.27, p=0.001, η_p^2=0.20; Figure 2.12a), with no main effect of session or any interactions in the main ANOVA model of acceptance rates (all p>0.1). One-sample t-tests revealed that effort level had a significant negative effect on choice, such that increasing effort decreased acceptance rates (session 1: $t_{(33)}$=8.55, p<0.001; session 2: $t_{(33)}$=6.05, p<0.001). Reward level also had a significant positive effect on choice, such that increasing reward increased acceptance rates (session 1:

$t_{(33)}$=6.11, p<0.001; session 2: $t_{(33)}$=5.34, p<0.001). Effort sensitivity decreased from session 1 to session 2 ($t_{(33)}$=2.17, p=0.04, d_z=0.37; Figure 2.12b). Reward sensitivity did not significantly differ between sessions (t(33)=0.08, p=0.941, d_z=0.01). The overall probability to accept an offer increased significantly from session 1 to 2 ($t_{(33)}$=2.59, p=0.01, d_z=0.44). All measures exhibited good-to-excellent reliability (Figure 2.12c).

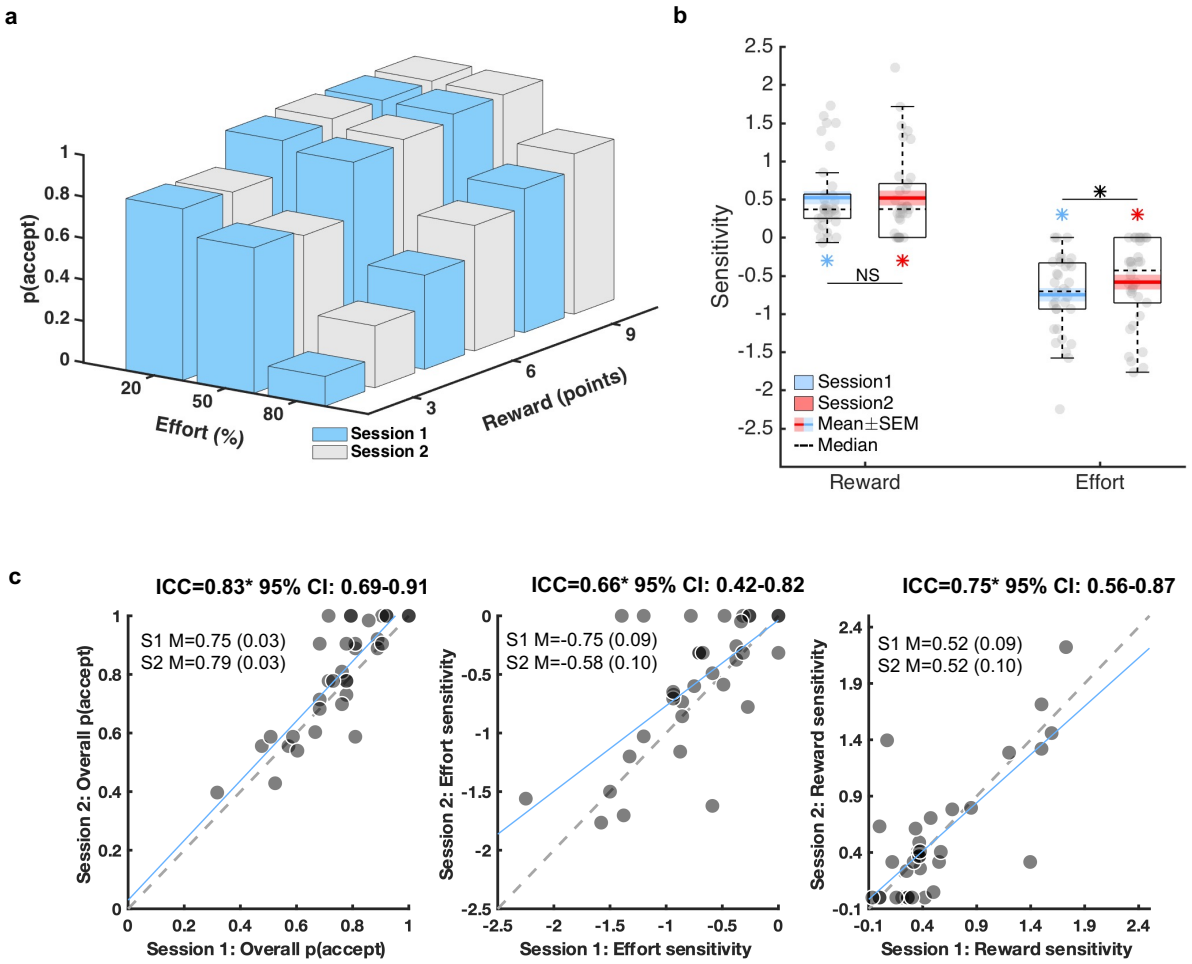

Figure 2.12 Basic behaviour, practice effects, and test-retest reliability of the physical effort task. The bar graph shows the probability to accept based on reward and effort levels in session 1 and 2 (a). Boxplots show linear contrast of the reward and effort levels on the probability to accept (b). Scatter plots and reliability of the physical effort task measures over session 1 and 2 are presented (c). Consistency (assesses relative ranking score over time) intraclass correlation coefficients (ICC) are presented. SEM: standard error of the mean; CI: confidence interval; S1: session 1; S2: session 2; M: Mean. Numbers in brackets represent standard error of the mean. *p<0.05.

2.4.3 Cognitive effort task (reward)

The probability to accept an offer was modulated by both the reward and effort magnitude (interaction: $F_{(2.088,102.29)}$=17.38, p<0.001, η_p^2=0.26; Figure 2.13a), with no main effect of session (p=0.51). As expected, increasing effort significantly decreased acceptance rates (session 1: $t_{(49)}$=4.96, p<0.001; session 2: $t_{(49)}$=4.65, p<0.001), while increasing reward displayed the opposite pattern (session 1: $t_{(49)}$=4.42, p<0.001; session 2: $t_{(49)}$=4.85, p<0.001). There was no effect of session on effort sensitivity (t(49)=0.74, p=0.46, d_z=0.11). However, reward sensitivity increased significantly on session 2 compared with session 1 (t(49)=2.43, p=0.02, d_z=0.34; Figure 2.13b), due to lower acceptance rates at low reward levels (Figure 2.13a). There was no effect of session on the overall probability to accept an offer (t(49)=1.37, p=0.18, d_z=0.19). Overall p(accept) exhibited fair reliability, and reward sensitivity good reliability, while effort sensitivity was not reliable over the two sessions (Figure 2.13c).

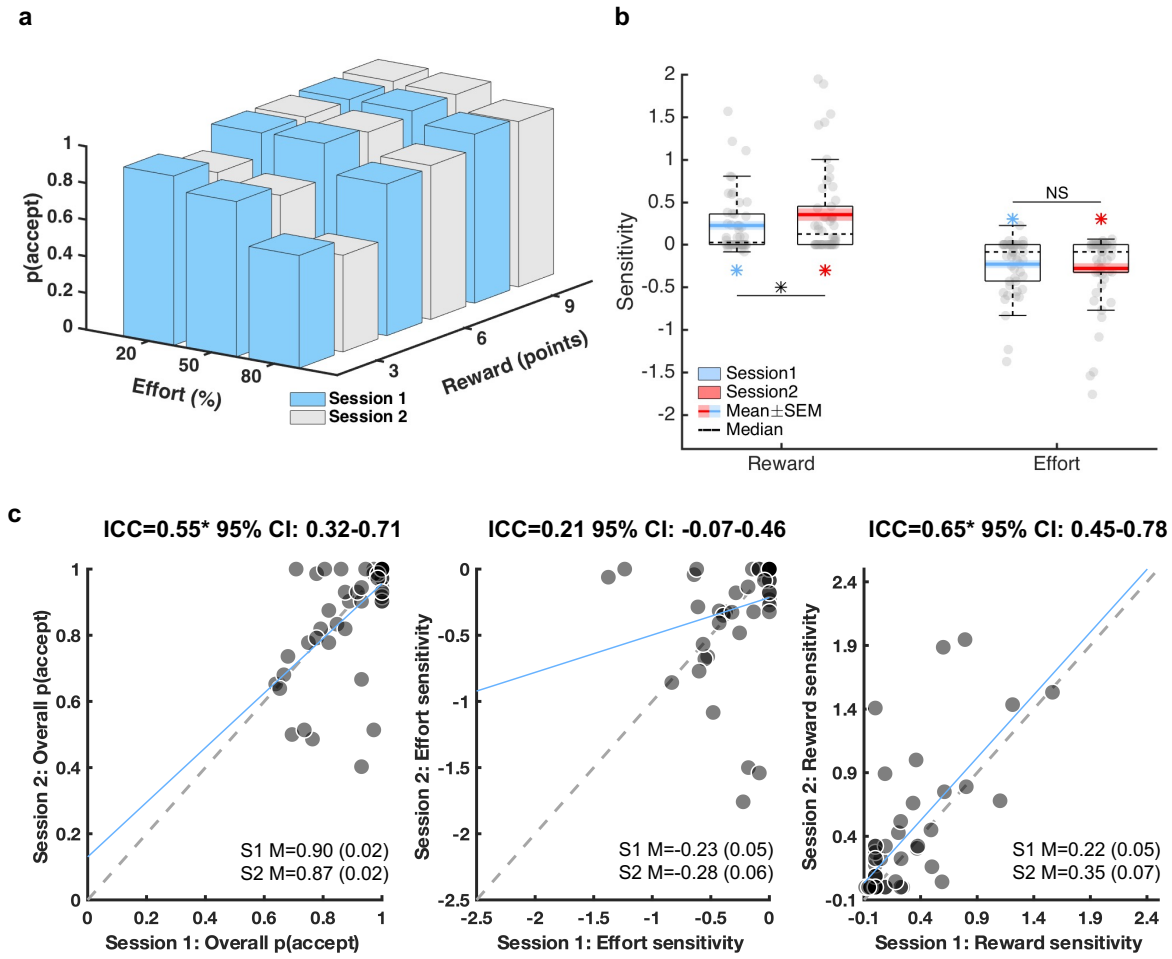

Figure 2.13 Basic behaviour, practice effects, and test-retest reliability of the cognitive effort reward task. The bar graph shows the probability to accept based on reward and effort levels (a). Boxplots show linear contrast of the reward and effort levels on the probability to accept (b). Scatter plots and reliability of the cognitive effort reward task measures over session 1 and 2 are presented (c). Consistency (assesses relative ranking score over time) intraclass correlation coefficients (ICC) are presented. SEM: standard error of the mean; CI: confidence interval; S1: Session 1; S2: Session 2; M: Mean. Numbers in brackets represent standard error of the mean. *p<0.05.

2.4.4 Cognitive effort task (punishment)

Decisions were influenced by a combination of punishment and effort magnitude (interaction: $F_{(1.53,68.92)}$=15.28, p<0.001, η_p^2=0.25; Figure 2.14a). As expected, effort had a significant negative effect on choice (session 1: t(45)=3.22, p=0.002; session 2: t(48)=3.31, p=0.002), and punishment had a significant positive effect on choice (session 1: t(45)=3.23, p=0.002; session 2: t(48)=3.05, p=0.004; Figure 2.14b). Effort sensitivity (t(45)=0.40, p=0.62, d_z=0.07), punishment sensitivity (t(45)=0.76, p=0.45, d_z=0.11), and overall probability to accept (t(45)=0.19, p=0.85,

d_z=0.03) did not significantly differ between sessions (Figure 2.14). However, overall acceptance rates were very high, limiting the sensitivity of these analyses. Punishment sensitivity exhibited fair reliability, while all other outcomes were not reliable (Figure 2.14c).

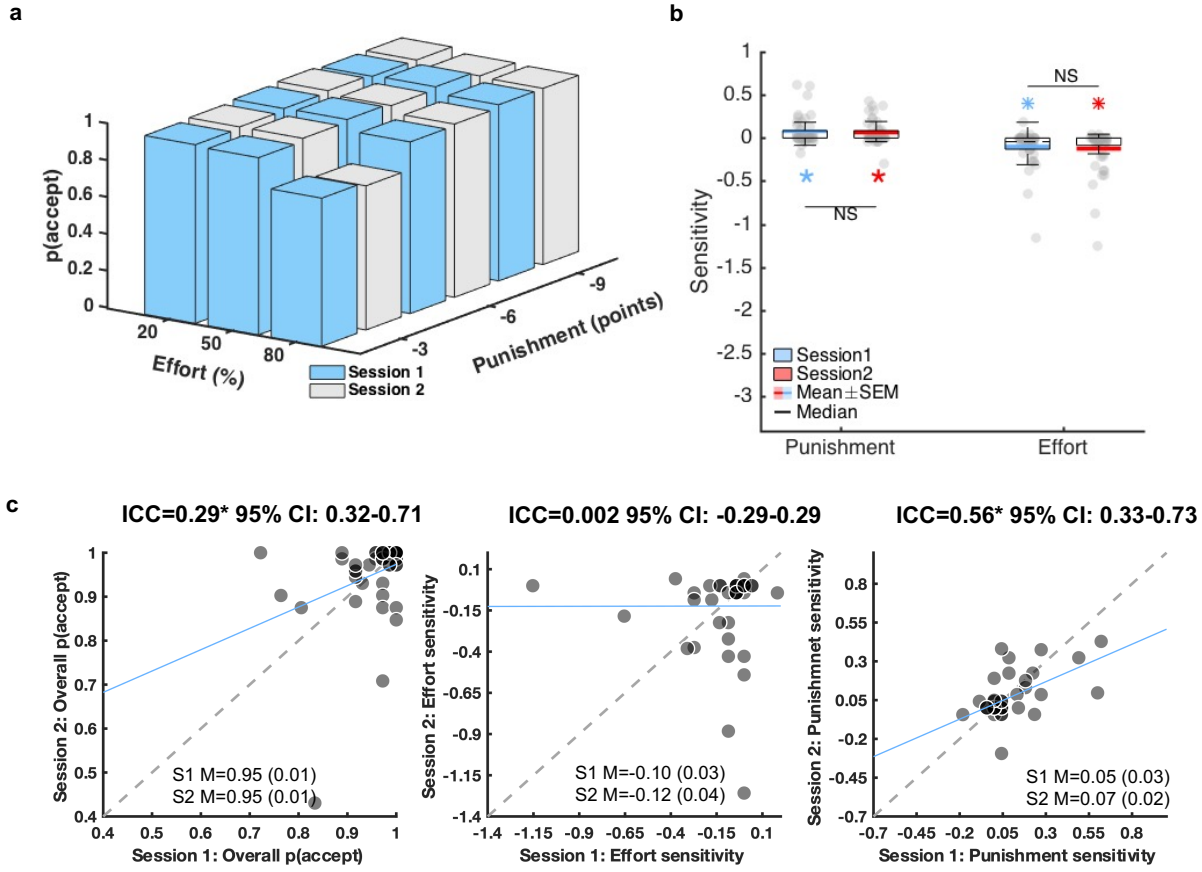

Figure 2.14 Basic behaviour, practice effects, and test-retest reliability of the cognitive effort punishment task. The bar graph shows the probability to accept based on punishment and effort levels (a). Boxplots show linear contrast of the punishment and effort levels on the probability to accept (b). Scatter plots and reliability of the cognitive effort punishment task measures over session 1 and 2 are presented (c). Consistency (assesses relative ranking score over time) intraclass correlation coefficients (ICC) are presented. SEM: standard error of the mean; CI: confidence interval; S1: Session 1; S2: Session 2; M: Mean. Numbers in brackets represent standard error of the mean. *p<0.05.

2.4.5 Investor-trustee task

As expected, betrayal of trust significantly influenced investment decisions ($F_{(1,49)}$=15.01, p<0.001, η_p^2=0.24), reflecting a decrease in the proportion invested immediately after participants were betrayed, compared with the average proportion invested throughout the task (Figure 2.15a). There was no significant effect of session (main effect: $F_{(1,49)}$=0.002, p=0.96, η_p^2<0.001; interaction: $F_{(1,49)}$=0.26, p=0.61, η_p^2=0.005). Sensitivity to betrayal of trust (difference

between the mean investment, excluding the betrayal trial, and the investment made immediately after the betrayal) showed poor reliability (Figure 2.15b). However, separately, these measures had higher reliability: $ICC_{MeanInvestment}$=0.84, $ICC_{InvestAfterBetrayal}$=0.44.

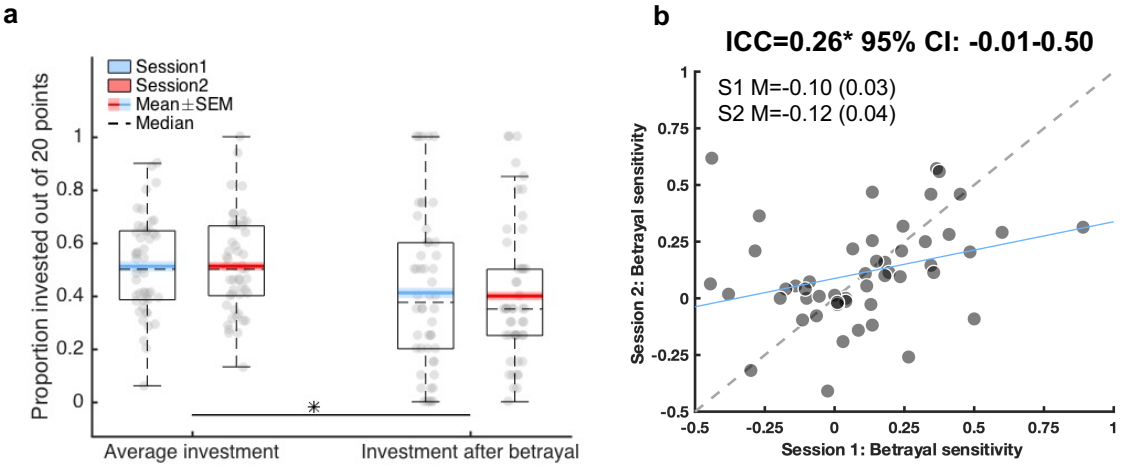

Figure 2.15 Basic behaviour, practice effects, and test-retest reliability of the investor-trustee task. Boxplots show the average proportion invested throughout the task (minus the betrayal trial) versus after the betrayal trial (a). Scatter plots and reliability of the investor-trustee task measures over session 1 and 2 are presented (b). Consistency (assesses relative ranking score over time) intraclass correlation coefficients (ICC) are presented. SEM: standard error of the mean; CI: confidence interval; S1: Session 1; S2: Session 2; M: Mean. Numbers in brackets represent standard error of the mean. *p<0.05.

2.4.6 Gambling task

2.4.6.1 Model-agnostic results

As expected, the propensity to gamble was significantly higher on mixed gambles ($F_{(1, 48)}$=13.71, p=0.001, η_p^2=0.22). There were no significant main ($F_{(1, 48)}$=0.76, p=0.40, η_p^2=0.02) or interaction ($F_{(1, 48)}$=1.07, p=0.31, η_p^2=0.02) effects of session on the propensity to gamble (session differences: probability to gamble on mixed trials $t_{(48)}$=0.23, p=0.82, d_z=0.03; probability to gamble on gain-only trials $t_{(48)}$=1.51, p=0.14, d_z=0.22; Figure 2.16a). Model-agnostic outcome measures on the gambling task exhibited good reliability (Figure 2.16b).

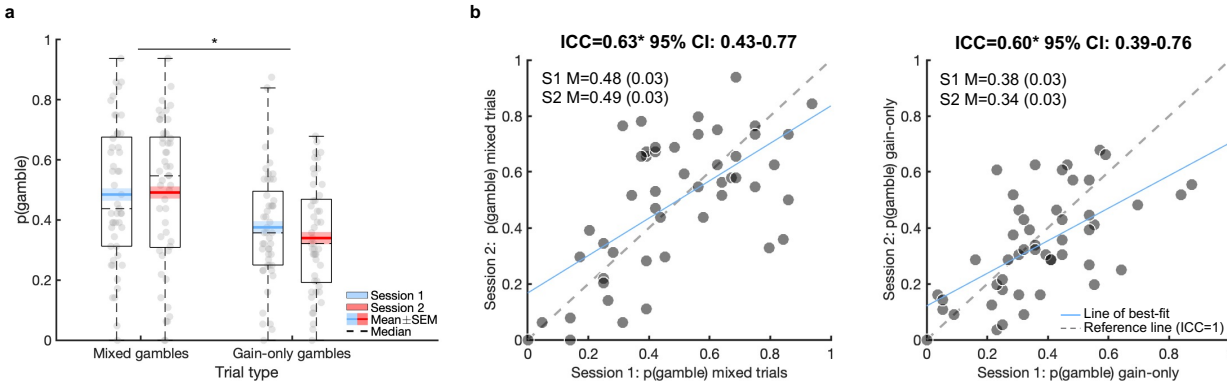

Figure 2.16 Basic behaviour, practice effects, and test-retest reliability of model-agnostic measures on the gambling task. Boxplots show the probability to gamble based on the trial type in session 1 and 2, with no significant session effects (a). Scatter plots and reliability of the gambling task model-agnostic measures over session 1 and 2 (b). Consistency (assesses relative score ranking over time) intraclass correlation coefficients (ICC) are presented. SEM: standard error of the mean; CI: confidence interval; S1: Session 1; S2: Session 2; M: Mean. Numbers in brackets represent standard error of the mean. *p<0.001.

2.4.6.2 Computational model

The winning model was the prospect theory model ('ra_prospect' in the hBayesDM package) with loss aversion, risk aversion and inverse temperature parameters (this last parameter represents choice consistency; Table 2.4), consistent with previous reports (Charpentier et al., 2017). A loss aversion parameter above 1 represents overweighting of losses to gains, while a risk aversion parameter less than 1 indicates aversion to risk. Model diagnostics indicated that this model performed well. All parameters showed high recoverability (Figure 2.17a), and synthetic data from the winning model accurately recapitulated real data (Figure 2.17b).

Model	S1: LOOIC	S2: LOOIC
Ra_prospect	**5249.68**	**5160.39**
Ra_noLA	6687.08	6551.38
Ra_noRA	6723.99	7167.25

Table 2.4 Model fits for the gambling task from the hBayesDM package. The winning model has the lowest Leave-One-Out Information Criterion (LOOIC) and noted in bold here. S1: Session 1; S2: Session 2.

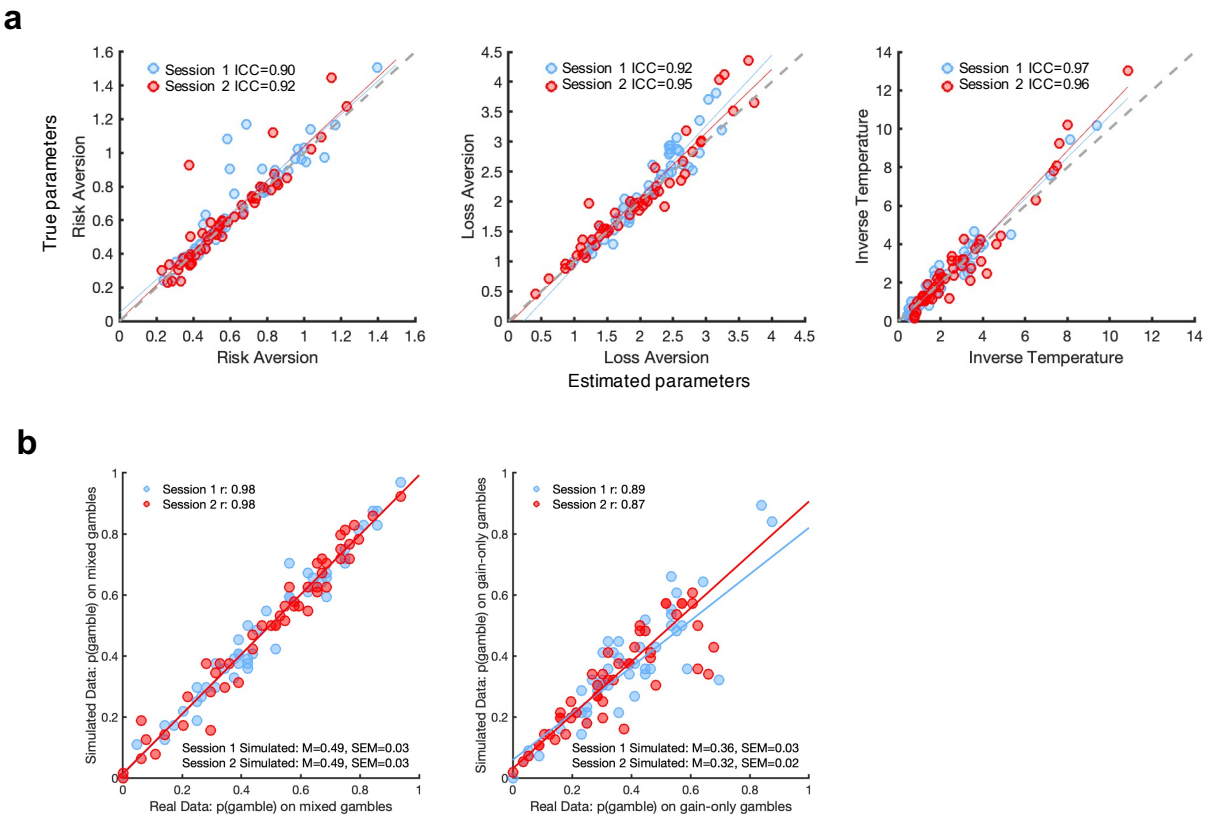

Figure 2.17 Model checks of the winning model from the gambling task. Plots show parameter recovery (a) and simulated against real participant data (b). Intraclass correlations (ICCs) represent two-way mixed model for single measures and absolute agreement. P(stay): probability to stay; M: mean; SEM: standard error of the mean; r: Pearson's correlations.

There were significant session effects on all prospect theory model parameters (on session 2: decreased loss aversion: $t_{(48)}$=2.17, p=0.04, d_z=0.31; decreased risk aversion: $t_{(48)}$=4.04, p<0.001, d_z=0.58; increased inverse temperature: $t_{(48)}$=3.07, p=0.004, d_z=0.44; Figure 2.18a). All estimated parameters demonstrated good-to-excellent reliability (Figure 2.18b). Neither test-retest nor practice effects were substantially altered, nor did any inferences change, when the model was fit under a single hierarchical prior.

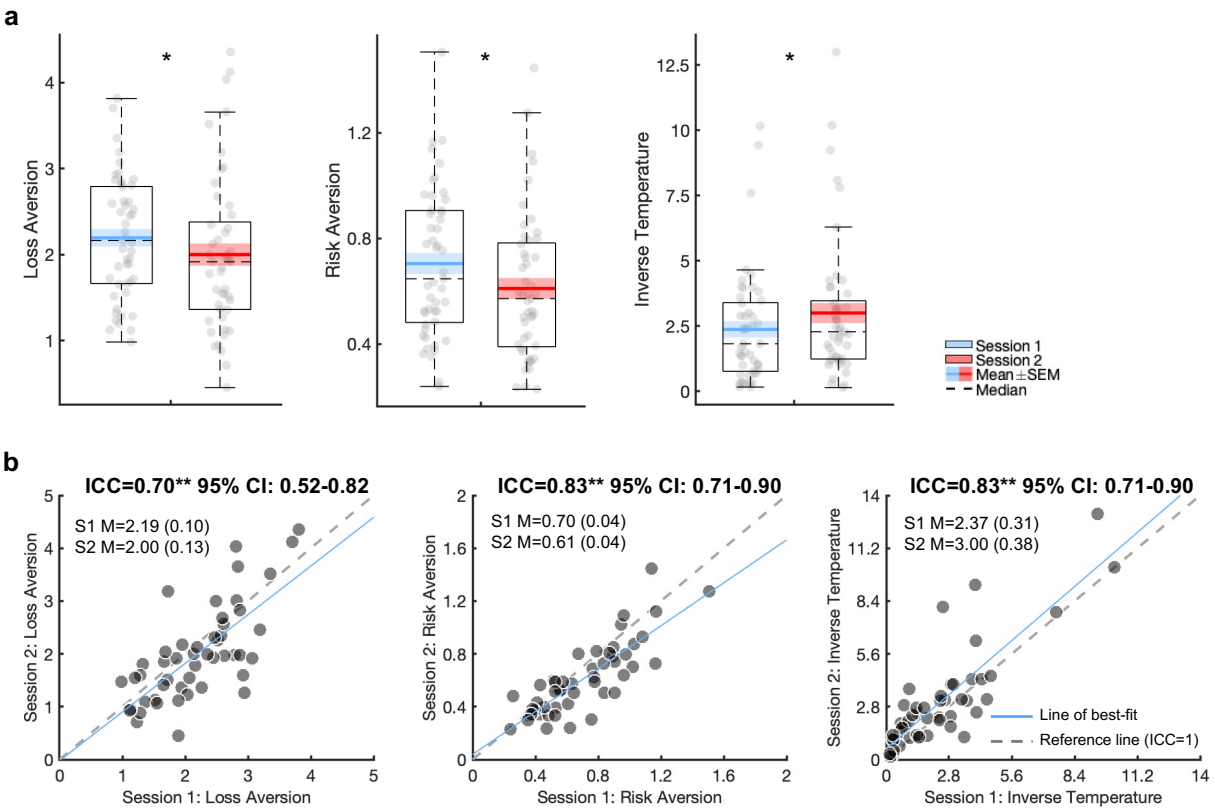

Figure 2.18 Practice effects and test-retest reliability of the prospect theory model derived from the gambling task. Boxplots show point estimates of the prospect theory model parameters in session 1 and 2, fit under separate priors (a). Scatter plots and reliability of the prospect theory model parameters over session 1 and 2 are presented (b). Consistency (assesses relative score ranking over time) intraclass correlation coefficients (ICC) are presented. CI: confidence interval; S1: Session 1; S2: Session 2; M: Mean. Numbers in brackets represent standard error of the mean. *p<0.05, **p<0.001.

Examining the future posterior predictive accuracy of the gambling task showed that the prospect theory model parameters from session 1 predicted future choices at session 2 significantly above chance (mean = 68%, chance = 50% accuracy; $t_{(48)}$= 12.08, p<0.001; Figure 2.19a). Predicting future performance at session 2 was significantly higher when based on participants' own parameter estimates from session 1 compared with model parameter estimates of other participants from session 1 ($t_{(48)}$=8.38, p<0.001; Figure 2.19b).

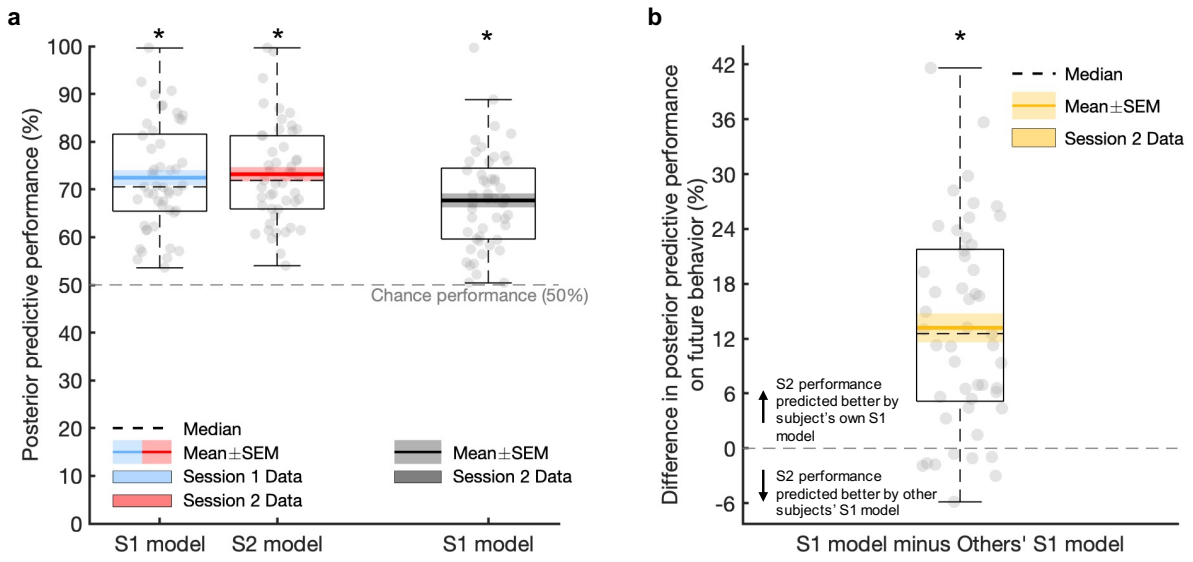

Figure 2.19 Posterior predictive performance of the prospect theory model derived from the gambling task. Boxplots depicting accuracy of prospect theory model in predicting choices (a). Session 1 (S1) model estimates predicted S1 behaviour significantly above chance (blue boxplot), as did session 2 (S2) model estimates on S2 data (red boxplot). Importantly, model parameter estimates from S1 predicted task performance from S2 above chance (black boxplot). Predicting future S2 performance using a participant's own S1 model parameter estimates was significantly better than using other participants' S1 model parameter estimates (b – zero indicates mean accuracy from other participants' parameter estimates). SEM: standard error of the mean. *p<0.001.

2.4.7 Clock task

Performance on the clock was significantly influenced by condition, such that go learning responses were significantly faster than no-go learning responses ($F_{(1,49)}$=142.59, p<0.001, η_p^2=0.74; Figure 2.20a). There was no significant main effect of session ($F_{(1,49)}$=0.04, p=0.85, η_p^2=0.001) or interaction ($F_{(1,49)}$=0.37, p=0.55, η_p^2=0.007) on learning. There was no significant session effect on overall RT swing either (t(49)=1.48; p=0.14, d_z=0.21; Figure 2.20b). Only the overall RT swing measure showed good reliability (Figure 2.20c). To better understand the poor reliability of the go and no-go learning measures, ICCs of the variables making up these measures (DEV, IEV and CEV conditions) were examined: ICC_{DEV}=0.10, ICC_{IEV}=0.56, ICC_{CEV}=0.19.

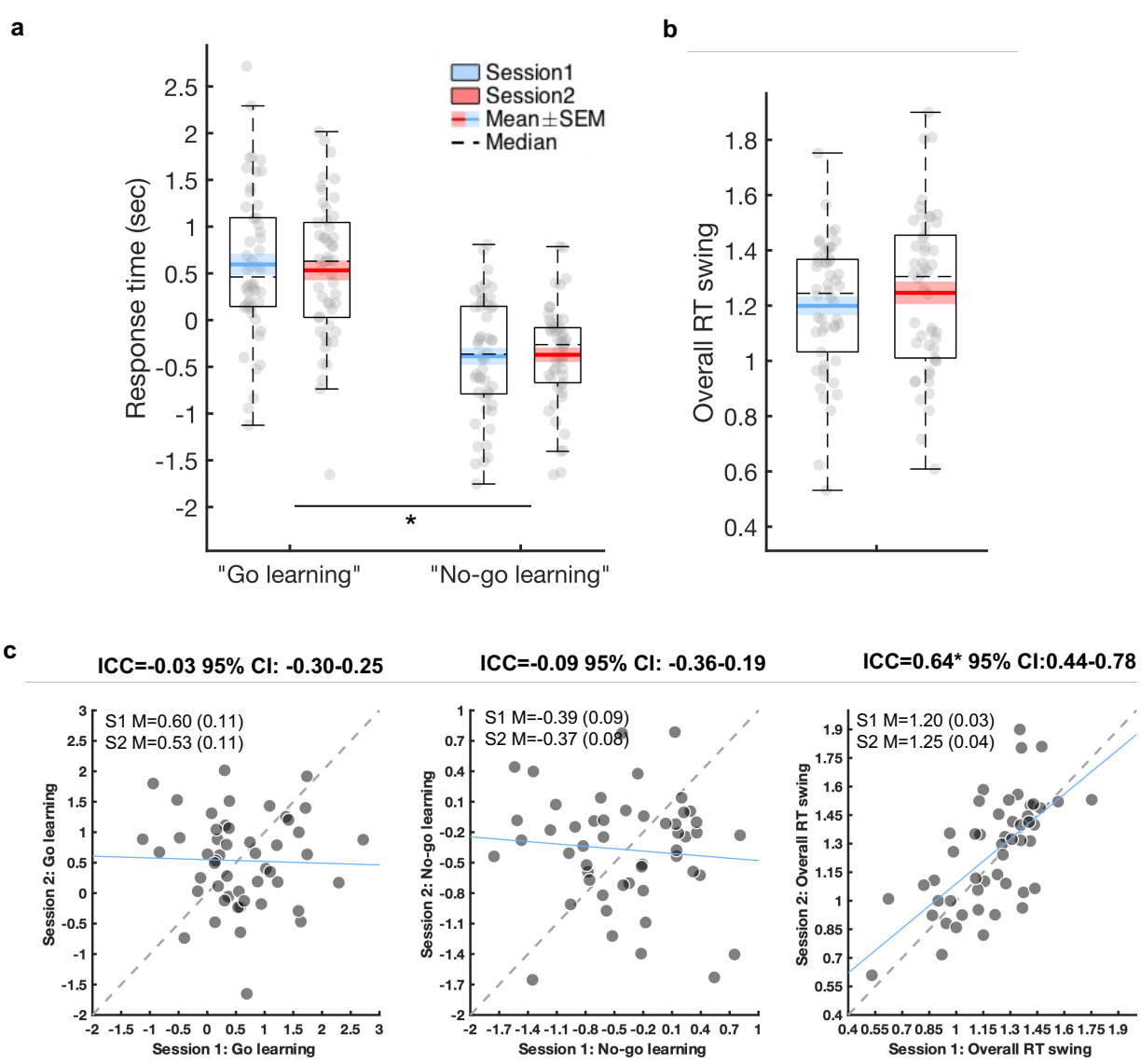

Figure 2.20 Basic behaviour, practice effects, and test-retest reliability of the clock task. Boxplots show go (mean RT difference between decreasing expected value and constant expected value condition) and no-go (mean RT difference between increasing expected value and constant expected value condition) learning (a) and overall RT swing in seconds, a measure of exploration (b). Scatter plots and reliability of clock task over session 1 and 2 are presented (c). Consistency (assesses relative score ranking over time) intraclass correlation coefficients (ICC) are presented. CI: confidence interval; S1: Session 1; S2: Session 2; M: Mean. Numbers in brackets represent standard error of the mean. *p<0.05

2.4.8 Exploratory analyses on effort tasks

Success rates for all tasks are presented in Table 2.5. There was a significant main effect of effort on success rates ($F_{(2,28.62)}$=71.20, p<0.001, η_p^2=0.72), such that all effort levels were

significantly different from each other (all p<0.006). There was also a significant session-by-success interaction ($F_{(2,29.05)}$=17.82, p<0.001, η_p^2=0.39), driven by a significant difference on success rates between the 50% and 80% effort levels (p<0.001). In the cognitive effort reward task, there was only a significant main effect of effort on success rates success rates ($F_{(2,82.31)}$=74.48, p<0.001, η_p^2=0.61), where each level was significantly different from each other (all p<0.004). Similarly, there was only a significant main effect of effort levels on success rates in the cognitive effort punishment task ($F_{(2,78.71)}$=94.36, p<0.001, η_p^2=0.68), where each level was significantly different from each other (all p<0.01). Finally, all tasks significantly differed from each other in all outcome measures (all p<0.05; Table 2.5).

Success rates						
Task	**20% effort Mean (SD)**		**50% effort Mean (SD)**		**80% effort Mean (SD)**	
	S1	**S2**	**S1**	**S2**	**S1**	**S2**
Physical effort	1 (0)	1 (0)	0.99 (0.03)	0.98 (0.04)	0.54 (0.31)	0.77 (0.20)
Cognitive effort reward	0.73 (0.20)	0.72 (0.18)	0.67 (0.20)	0.69 (0.20)	0.46 (0.24)	0.52 (0.25)
Cognitive effort punishment	0.72 (0.18)	0.75 (0.16)	0.70 (0.19)	0.69 (0.17)	0.45 (0.03)	0.51 (0.03)
Outcome measures, across sessions, for all effort task measures						
Task	**p(accept) Mean (SD)**		**Effort sensitivity Mean (SD)**		**Valence sensitivity Mean (SD)**	
Physical Effort	0.77 (0.03)		-0.67 (0.08)		0.52 (0.09)	
Cognitive effort reward	0.86 (0.02)		-0.27 (0.05)		0.37 (0.08)	
Cognitive effort punishment	0.95 (0.01)		-0.12 (0.03)		0.06 (0.03)	

Table 2.5 Exploratory effort analyses. S1: Session 1; S2: Session 2. SD: Standard deviation. Note that N=34 in the analysis examining if measures between effort tasks were significantly different from each other, as some participants did not complete the physical effort task which was added part-way through the study.

2.4.9 Exploratory correlations

There were no significant correlations (following Bonferroni correction) between any of the task measures and gender (all t<1.99, all uncorrected p>0.05), age or years of education (all absolute r-values <0.34, uncorrected p>0.01). The strongest association was observed between age and the punishment learning rate parameter from the four-armed bandit task (r=0.33, uncorrected p=0.02), with no other associations showing significant effects at an uncorrected level.

2.5 Discussion

The primary aim of this Chapter was to assess the psychometric properties of several tasks examining different aspects of reward and punishment processing such as learning, valuation, and motivation. Overall, task performance was as expected on all tasks and several tasks showed acceptable reliability, indicating translational potential of clinically-relevant measures. However, test-retest reliability varied substantially across and within tasks, highlighting the complexities of translating tasks to the clinic and using them in within-subjects designs.

2.5.1 Reliability of learning and valuation tasks

The reliability of model-agnostic measures across tasks measuring learning and valuation were generally mixed. For example, the bandit and clock task likely both incorporate aspects of learning and valuation into their model-agnostic measures (these processes can only be separated using computational models). However, only the bandit task demonstrated good reliability across its model-agnostic measures, while go and no-go learning in the clock task showed poor reliability. It is not entirely clear what this discrepancy in reliability stems from. One obvious difference between the tasks is in the modality of measures: choices in the bandit versus response times in the clock task. However, the investor-trustee task also encompasses elements of learning based on choices and showed similarly poor reliability as the clock task. However, the poor reliability in the investor-trustee task may have stemmed from participants knowing about the betrayal in their second session, and thus adjusting their behaviour.

It has been suggested that one factor contributing to poor reliability is the use of difference scores (Hedge et al., 2018). The components making up the difference score tend to be highly correlated and thus the individual measurement errors are combined in the difference score. Difference scores tend to reduce variance between participants, such that the measurement error is increased relative to the between-subject variance. It then follows that the reliability will decrease as the between-subject variance is the numerator, and the measurement error is the denominator in the ICC calculation (Eq. 1). It is possible that the poor reliability in the clock and investor-trustee task may stem from this limitation as both used difference scores. Indeed,

when examining the ICCs of the components of the difference scores, these were generally higher for the clock and investor-trustee task. However, the model-agnostic measures from the bandit task were also based on difference scores, and the components making up the difference score of the clock task were still in the range of poor-to-fair reliability. Thus, it is not entirely clear whether difference scores contributed much to the lower reliability of the clock task. It has also recently been recognised that, in contrast to the popularly held belief that difference scores have low reliability (Thomas & Zumbo, 2012), this is not always the case when incorporating estimates of variability (Chiou & Spreng, 1996; Trafimow, 2015), supporting the findings of the current paper. In addition, many latent processes may contribute to the model-agnostic measures of which some may be reliable. Thus, to establish if these processes indeed reflect poor reliability, modelling of them should be considered.

Interestingly, RT swings, an index of exploration, in the clock task exhibited good reliability, suggesting that the clock task may still be suitable to assess uncertainty-driven exploration in repeated-testing contexts. Goal-directed exploration on the clock task has previously been associated with anhedonia (Strauss et al., 2011), suggesting that this measure in particular may be suitable for assessing the mechanisms of ketamine in a clinical trial.

2.5.1.1 Reliability of computational models

Overall, most parameters reflecting RL and decision-making processes exhibited adequate reliability and the winning models predicted future performance well. These results provide promise for their use in clinical settings and within-subjects designs. However, this conclusion again depends on the specific parameters assessed in each task.

Reinforcement model: In contrast to our hypotheses, the computational measures of the bandit task exhibited similar reliability to the model-agnostic outcome. Reward and punishment learning rates from the bandit task demonstrated good reliability while reward and punishment sensitivity showed fair reliability, suggesting that this task may be more suitable for assessing learning rates than sensitivity. These results are however in contrast to previous studies

showing poor reliability of reward/punishment tasks with a learning component (Bland et al., 2016; Moutoussis et al., 2018). These differences may arise for a multitude of reasons, including the parameter estimation method. Importantly, however, we provide evidence that it is possible to achieve at least moderate reliability for some canonical RL parameters. As elevated punishment learning rates (faster learning in the face of negative outcomes) have been associated with greater mood and anxiety symptoms (Aylward et al., 2019), these results suggest that this parameter may be appropriate for use as a potential measurable mechanistic treatment target.

The lapse parameter has also previously been associated with mood disorders (Aylward et al., 2019). However, in line with a previous study (Moutoussis et al., 2018), this parameter exhibited poor reliability. This parameter measures responding not captured by the model (including goal-directed and random exploration) and the sources of this 'noise' might differ across sessions. It is therefore perhaps unsurprising that this parameter was unreliable. Crucially, the lapse parameter showed poor recoverability, which places an upper limit on its potential reliability. Some of this poor recoverability may be explained by limited lapse variation, especially in session 1. This suggests that the lapse parameter could be replaced with a constant.

Prospect theory model: All parameters from the gambling task showed good-to-excellent test-retest reliability. These were also substantially higher than the reliability of the model-agnostic measures, suggesting that computational models may offer advantages in psychometric properties, in addition to their advantage in specifying mechanisms. In particular, the risk aversion parameter, which has previously been associated with clinical anxiety (Charpentier et al., 2017), exhibited excellent reliability (ICC>0.8), providing promise for use in clinical research and within-subjects designs. These results are consistent with previous studies, but we generally found considerably higher reliability than previously reported (previous reliability reports: loss aversion r≈0.25-0.61, risk aversion r≈0.50-0.60, inverse temperature r≈0.30-0.60) (Chung et al., 2017; Glockner & Pachur, 2012; Scheibehenne & Pachur, 2015). These studies all

used different estimation procedures, including hierarchical Bayesian, and employed both longer and shorter testing time-windows than the current study, suggesting that these factors may not fully explain the differences. It is possible that our results instead stem from different prospect model specifications (Chung et al., 2017; Glockner & Pachur, 2012; Scheibehenne & Pachur, 2015), as well as different task designs.

The mean loss and risk aversion parameters observed are consistent with previous literature indicating that losses are weighed about twice as much as gains, and that people are on average risk averse (Kahneman & Tversky, 1979; Schonberg et al., 2011; Sokol-Hessner & Rutledge, 2019; Tversky & Kahneman, 1992). Indeed, prospect theory models have shown to be highly replicable across different contexts (Ruggeri et al., 2020). Our implementation of the gambling task may therefore represent a case where group-average results are highly reproducible, but the task is also suitable to assess individual differences. It has been observed that this is rarely the case, since tasks that are designed to produce reliable average effects do so by minimizing between-subject variance, whereas what makes tasks reliable and suitable for inter-individual assessments are large between-subject but small within-subject variances (Hedge et al., 2018). This may have occurred because of the calibrated design of the present gambling task. A similar approach of dynamically updating parameter values to each individual during task performance has previously been suggested as a solution to unreliable cognitive tasks (Palminteri & Chevallier, 2018).

Future predictive accuracy: In addition to examining reliability using the traditional ICC method, we also examined how well the models predicted future task performance. This approach provides a complementary perspective on reliability, which is unique to computationally-informed measures. Generative models were consistently able to predict participants' future behaviour above chance. Notably, participant's own parameter estimates from the first session were on average better at predicting their future performance compared with using parameter estimates from all other participants. This indicates that individuals do indeed differ reliably in the cognitive mechanisms underlying their decisions, and offers reassurance that hierarchical

estimation procedures are suitable for estimating inter-individual inferences (Brown et al., 2020; Daw, 2011; Scheibehenne & Pachur, 2015). In other words, individuals show relatively idiosyncratic but consistent computational decision-making profiles. This is consistent with two previous studies using a different prospect theory model and gambling task (Glockner & Pachur, 2012; Scheibehenne & Pachur, 2015).

Practice effects: Some of the reliable parameters showed small-to-medium practice effects. Practice effects can either obscure a true effect or lead to false treatment claims if appropriate controls are not employed. Quantifying session effects allows such changes to be accounted for. In the RL model, reward sensitivity increased in the second session, while all other reliable RL processes were fairly stable. In contrast, all prospect theory parameters showed significant session effects. However, the sensitivity analysis showed no substantial practice effects of RL parameters when data were fit under a single prior, while the practice effects on prospect theory parameters remained. Thus, the apparent practice effects on the RL task should be interpreted with caution, as these may be overestimated under the two-prior estimation approach (Valton et al., 2020). Importantly, the ICC estimates were hardly influenced by the estimation approach. Although practice effects were evident in the computational parameters, no clear changes were observed in the model-agnostic measures, suggesting further that model-agnostic measures lack the precision to quantify these decision-making processes.

2.5.2 Reliability of effort tasks

Motivational deficits have consistently been associated with both MDD and anhedonia, underlining the importance of investigating these concepts in the mechanisms of ketamine's beneficial effects (Husain & Roiser, 2018). Here we assessed three adaptations of effort tasks exploring motivation through physical effort, and cognitive effort to win rewards or to avoid punishments.

Only the physical effort task showed reliability across all measures. Both overall probability to accept, and reward sensitivity exhibited excellent test-retest reliability, while good reliability

was observed for effort sensitivity. However, effort sensitivity decreased over sessions (albeit with a relatively modest effect size), while the overall probability to accept increased in the second session. Reward sensitivity did not significantly change between sessions, suggesting that the session effect seen in the overall p(accept) measure is primarily due to lower discounting of high effort levels. Since greater effort sensitivity has been associated with greater symptoms of apathy on this task (Bonnelle et al., 2016; Bonnelle et al., 2015), this effect is particularly worth considering in the context of a ketamine trial. If the anti-anhedonic effect of ketamine is equal to or lower than the practice effect, then this would suggest that no improvement in effort sensitivity was observed. However, previous studies have shown a large effect size of ketamine's anti-anhedonic effect (Lally et al., 2014), suggesting that the anti-anhedonic effects may still be observable. It is possible that the reduced effort sensitivity on the second testing session stems from the increase in success rates of the hardest effort level between sessions. Improving this task design limitation may therefore abolish the effort sensitivity practice effects.

In contrast to the physical effort task, effort sensitivity in the cognitive effort reward task showed poor reliability with fair-to-good reliability on reward sensitivity and overall p(accept). The poor reliability of effort sensitivity seems to be driven by a number of individuals who were either very strongly sensitive or insensitive to effort on their first session, but showed the opposite pattern on their second session. This could reflect regression to the mean effects (Barnett et al., 2005). A similar relationship in effort sensitivity can be detected for a number of subjects in the cognitive effort punishment task, where neither effort sensitivity nor overall p(accept) was reliable.

It is worth considering why effort sensitivity was reliable in the physical but not cognitive tasks. This may be due to the differences in the respective task designs. In the physical task, the time-window of the effort execution was constant whereas in the cognitive tasks it terminated if an error was committed. This might suggest that effort was not perceived as very costly in the cognitive effort tasks, simply because a failure resulted in no effort execution. Indeed, overall

acceptance rates were greater in the cognitive effort tasks, compared with the physical task. Sensitivity to differences in effort magnitude was also lower in the cognitive effort tasks, despite low success rates in the cognitive tasks. A possible explanation is that participants' decisions were influenced by different factors in the two effort tasks, possibly unrelated to effort valuation in the cognitive effort tasks. Future studies should therefore address this aspect of the cognitive effort design. Additionally, success rates on the high effort level were relatively low across tasks, which might have induced a risk confound. One way to address this would be to lower the effort levels and/or make the calibration easier.

The results could also be due to differences between effort domains. It is as yet unclear if similar mechanisms underlie cognitive and physical effort. While some suggest that they are distinct (Croxson et al., 2009), others have found domain-general processes (Chong et al., 2017; Schmidt et al., 2012). In the present study all effort tasks significantly differed on overall accept, effort and reward sensitivity, suggesting different modulatory effects of both effort and valence domains. However, considering the above design limitations, these results are preliminary and should be interpreted with caution.

Furthermore, both cognitive effort tasks exhibited very high overall acceptance rates (>0.85), especially the cognitive effort punishment task (0.95). This suggests that task performance was at ceiling and these tasks may thus not be sufficiently sensitive to probe individual differences in motivational processes. The cognitive effort tasks thus need further refinement before use, and therefore their reliabilities should be interpreted cautiously. However, the physical effort task shows strong potential for repeated-testing purposes, which is in line with other studies suggesting relatively good reliability of physical effort tasks (Ohmann et al., 2022; Reddy et al., 2015).

2.5.3 Limitations

A number of limitations of this study merit comment. The main limitation concerns the analysis approach to derive the outcome measures. The majority of tasks were designed to be analysed

with computational models, as these have the advantage of uncovering specific processes that contribute to behaviour that cannot be examined with model-agnostic summary statistics (Adams et al., 2016; Huys et al., 2016; Teufel & Fletcher, 2016). This limitation is particularly pertinent to the clock task as it was only possible to examine crude measures of learning/valuation and exploration as there is currently no model implemented for the clock task in hBayesDM. As such, inferences are limited to the chosen outcome measures here.

Another factor to consider is the nature of the sample. Test-retest reliability of tasks in healthy individuals may differ from other population groups, especially clinical groups. This is worth considering since the goal is to apply these tasks in a clinical trial with both healthy and depressed individuals. Nevertheless, patient groups tend to show greater variability between individuals, which could potentially increase test-retest reliability in such populations (Palmer et al., 2017; Paulus et al., 2016).

Finally, no measures were correlated with any demographic measures following correction for multiple comparisons, suggesting no evidence for associations with general cognitive abilities (although IQ was not directly assessed). This also suggests that if confounds do exist for age, gender, or years of education, they are likely to be relatively weak, which is important for clinical use.

2.5.4 Conclusions

In summary, the current study is an important first step in investigating the reliability of reward and punishment processes. The results suggest that several tasks across learning, valuation and motivation processes have adequate test-retest properties, but these conclusions depend on the specific outcome measures assessed. In particular, the four-armed bandit, gambling and physical effort tasks are fit to assess all their key measures in within-subjects designs, while the clock task may only be suitable for examining exploration. The investor-trustee may not be suitable for repeated-testing at all, and the present cognitive effort tasks need further fine-tuning. Of note, computational RL reward and punishment processing parameters showed

similar reliability to their model-agnostic counterparts, while prospect theory risk/loss aversion parameters model exhibited substantial improvements over model-agnostic measures, illustrating the advantage of modelling behaviour for these processes. Overall, these results suggest that a multitude of reward and punishment processes, across model-agnostic and model-derived parameters can be measured reliably, encouraging their use in clinical trials.

3 The spatiotemporal dynamics of motivation to exert cognitive effort: a simultaneous EEG-fMRI study

3.1 Abstract

Motivation to exert cognitive effort might be an important process underlying anhedonia, and by extension aspects of the anti-anhedonic effects of ketamine. Although a ubiquitous process, relatively little is known about the neural spatiotemporal dynamics involved in cognitive effort-related decisions. Few prior studies have specifically examined the neural mechanisms involved in reward and cognitive effort sensitivity independently. In this study healthy participants (N=22) completed a novel cognitive effort-based decision-making task, adapted from the design presented in Chapter 2, during simultaneous EEG-fMRI recording. As expected, decisions to exert cognitive effort increased with increasing reward levels and decreased with increasing effort levels. In the EEG analysis we found a parietal ERP peak around 220-280ms after offer presentation that was sensitive to decisions about effort costs, but not reward magnitude. In the fMRI analysis distinct regions were modulated by effort during decisions to accept an offer, in a quadratic manner. These included both regions previously shown to be important for physical effort, such as the ACC, and regions known to be important for higher-order cognitive processes such as dorsolateral PFC (dlPFC) and ventrolateral PFC (vlPFC). However, in a parametric analysis the identified ERP component could not be localised to any of these or other neural regions. These findings indicate that specific PFC regions are sensitive to decisions involving cognitive effort cost, and decision-related activity may emerge relatively early during effort-based decision making, around 200-300ms after offer presentations.

3.2 Introduction

Every day we are faced with situations that require exerting effort to obtain rewards. These range from the trivial, such as getting up from the sofa to find a cookie in the kitchen, to the more involved, such as planning the number of steps and possible outcomes in a game of chess. Effort-based decision making seems to be particularly affected in MDD and other psychiatric disorders that have a strong motivational component (see Chapter 1). Most tasks examining effort-based decision making for reward have focused on physical effort. While this undoubtedly maps onto behaviours related to difficulty in motivation, it ignores the important domain of cognitive effort.

Like physical effort, cognitive effort has been conceptualised in neuroeconomic terms, providing a useful account of how potential costs and benefits drive decisions to engage in effortful behaviour (Westbrook & Braver, 2015). Several experiments manipulating cognitive effort using various taxing cognitive functions, including task switching (Kool et al., 2010; McGuire & Botvinick, 2010), spatial attention shifts (Apps et al., 2015; Chong et al., 2017), and working memory (Westbrook et al., 2013), have shown that people are averse to cognitively demanding tasks (Kool & Botvinick, 2014; Kool et al., 2010). A consistent finding is that human participants will routinely forego money in order to avoid exerting cognitive effort, and indeed even incur physical pain (Vogel et al., 2020). These studies have further revealed that willingness to engage in cognitive effort varies considerably between individuals, which is associated with a variety of demographic and neurobiological factors (Hofmans et al., 2020; Westbrook & Braver, 2015; Westbrook et al., 2020). However, current cognitive effort paradigms do not adequately dissociate reward benefits and effort costs, and other potential confounds in existing paradigms, such as temporal and probability discounting, can complicate interpretations.

Much of our understanding of the neural basis of motivated effort has emerged from physical effort paradigms. Several studies indicate that the willingness to exert effort depends on a distributed network of brain regions, including the striatum, vmPFC, ACC/dorsomedial (dm)PFC,

and anterior insula (Husain & Roiser, 2018). For example, reward computations at the decision-phase during a physical effort task appear to activate the vmPFC and striatum, whereas decisions about physical effort activate motor areas, ACC and insula (Bonnelle et al., 2016; Hauser et al., 2017; Klein-Flügge et al., 2016). Interestingly, apathy has been associated with physical effort-related dmPFC and ACC activity in healthy individuals (Bonnelle et al., 2016; Hauser et al., 2017) and in children with a history of maltreatment, who show high levels of apathy (Armbruster-Genç et al., 2022). Most relevant to the current thesis, ketamine's anti-anhedonic effects are associated with changes in ACC metabolism (Lally et al., 2014; Lally et al., 2015), and it has recently been hypothesised that the ACC may function as a hub in mediating ketamine's antidepressant action (Alexander et al., 2021) . Although fMRI provides excellent spatial resolution, and thus insight into which neural regions may be involved in decisions about effort, much less is known about the temporal dynamics of the neural processes underlying effort-based decision-making.

In this regard, two event-related potentials (ERPs) are of particular interest: the N2 and P3. The N2, a negative frontocentral ERP peaking around 200ms following cue onset, has been shown to be important for cognitive control processes (Glazer et al., 2018). For example, the N2 amplitude may increase with perceived effort on a go/no-go task (Benikos et al., 2013), suggesting that this component might be sensitive to effort costs. However, these studies typically examined the N2 component during the execution of cognitively effortful processes (Folstein & Van Petten, 2008); thus, its role during decisions about effort is less clear, and to our knowledge has not been examined. Interestingly, this component has been suggested to be generated in the ACC (Baker & Holroyd, 2011). However, this conclusion is predominantly based on source localization techniques, which are fraught with spatial precision problems (Hallez et al., 2007).

The P3, a positive parietal ERP peaking around 300-700ms post-stimulus (Fabiani et al., 1987), has shown to respond to motivational incentives (Kleih et al., 2010). For example, greater P3 amplitude has been associated with greater reward incentives in motivational contexts

(Goldstein et al., 2006; Hughes et al., 2013; Zhang et al., 2017). Reward-anticipation-related P3 activity may be related to both the ventral striatum (Pfabigan et al., 2014) and vmPFC (Giustiniani et al., 2020). Interestingly, in one study P3 magnitude, measured during the anticipatory stage of the monetary incentive delay (MID) task, was correlated with the probability to accept harder effort trials in the EEfRT (EEG was not recorded during the EFfRT itself in this study) (Zhang et al., 2017), suggesting that the P3 might be sensitive to motivation to exert effort. However, it is not clear whether the P3 signals overall motivation or is specific to reward or effort evaluations. Interestingly, the P3 may also be associated with motivational symptoms such as apathy and anhedonia (Dubal et al., 2000; Takayoshi et al., 2018).

Collectively, these studies point to a set of fronto-striatal regions that might be important in signalling effort costs and reward benefits during decision-making. However, the neural computations subserving decisions about cognitive effort remain much less clear, particularly as existing tasks do not adequately parameterise reward and effort. Although some studies have examined the neural mechanisms of cognitive effort, these have typically only focused on the overall subjective value of options, i.e., the integration of rewards and efforts during decisions (Apps et al., 2015; Chong et al., 2017). Thus, the mechanisms underlying cognitive effort and reward sensitivity during decisions remain unclear, as differences in the subjective value of options could be driven by either or both. Moreover, it is unclear whether reward benefits and cognitive effort costs have temporally dissociable influences on effort-related decisions.

The main aim of the current study was therefore to characterise the spatiotemporal neural activity during decisions to engage in cognitive effort using a novel cognitive effort task, by employing the complementary strengths of EEG and fMRI. Concurrent EEG-fMRI is however technically challenging, and thus the goal of the current study was to pilot the experimental set-up and explore the spatiotemporal dynamics of neural mechanisms of cognitive effort in a pilot study. It was predicted that: 1) behaviourally, motivation to exert effort would increase with reward incentives and decrease with effort costs; 2) effort computations during decisions to accept would be positively associated with the N2 ERP and ACC activation, while reward would

positively scale with the P3 ERP, striatal and vmPFC activation; and 3) the neural generator of the N2 would be the ACC, while the P3 would be associated with striatal and vmPFC activation.

3.3 Methods

3.3.1 Participants

Twenty-six healthy, right-handed, participants were recruited from the UCL Institute of Cognitive Neuroscience participant database. Participants completed a novel cognitive effort decision-making task during simultaneous EEG-fMRI recording. Four participants were excluded due to poor data quality in either the fMRI or EEG modality (final N=22: 13 females [65%]; age range=20-50; mean age=26.40, SD±7.88 years; mean education=17.64, SD=±2.44 years). Participants reported no current or past psychiatric or neurological disorder; no cannabis use in the 31 days prior to testing; no alcohol consumption in the 24 hours prior to testing; no recreational drug use in the week prior to testing; and no MRI contradictions. All participants provided written informed consent and were compensated £40 and a bonus of up to £10 based on task performance. The study was approved by the UCL Psychology and Language Sciences Research Ethics Committee (Project ID Number: fMRI/2013/005).

3.3.2 Behavioural data

3.3.2.1 Task design

A similar cognitive effort reward task as employed in Chapter 2 was used. The task was modified to address a number of limitations. These mainly involved reducing ceiling effects and increasing success rates across effort levels. On each trial, participants were initially presented with the number of points available, and the effort level exertion required to obtain the reward (Figure 3.1). They were free to accept or reject the offer. If an offer was rejected, the cognitive effort challenge was skipped, and a feedback screen displayed 'No response required'. If an offer was accepted, participants were required to complete the cognitive effort challenge, which involved correctly categorising ten numbers (0-9) in a sequence as odd or even (0 categorised as even) under time pressure. Effort was manipulated by changing the time pressure, with less time allowed to complete the categorisation task at higher effort levels.

Based on piloting, the odd/even categorisation challenge was modified from Chapter 2 to require participants to complete the categorisation of all ten numbers even if mistakes were

made or the time limit had been exceeded. This modification was implemented to increase the sensitivity to effort, as in the previous version a single mistake would automatically terminate the challenge. If an error was made during the effort exertion (i.e., miscategorising a number), the number turned red, and the participant had to correct the error before the next number would appear, with correct responses turning green. In addition, one mistake was allowed in each "successful" sequence (incorrect sequences were not rewarded). This was implemented to increase success rates.

The task was further adapted for use during simultaneous EEG-fMRI. The offer screen was divided into two parts such that one piece of information (reward or effort) was presented initially, with the second part of the offer (effort or reward) added to the screen one second later (Figure 3.1). This was implemented to allow for processing of both pieces of information before a decision was reached. The order of presentation was counterbalanced across participants (i.e., half of the participants were presented with the reward information initially, the other half with the effort information). The response screen was further separated from the offer screen in order to dissociate the motor response from the decision computation (Klein-Flügge et al., 2016). The presentation side of 'Y' (accept offer) and 'N' (reject offer) was randomised within participants and appeared on each side (left/right) 50% of the time. This was introduced to reduce any motor preparatory activity during the decision phase, as participants could not anticipate which key they needed to press before the choice screen. Half of the accepted trials additionally skipped the effort challenge to reduce the task administration time and possible fatigue effects, as in previous studies (e.g., Klein-Flügge et al., 2016). However, participants were informed that they would have to complete these trials outside of the scanner.

Prior to scanning, participants completed a practice session outside the scanner to become familiarised with the task. There were three levels each of reward and effort. These were presented to participants as 'low reward', 'medium reward', 'high reward' and 'low effort', 'medium effort' and 'high effort'. These descriptors were used to increase the sensitivity to

what each participant may perceive as 'low', 'medium' and 'high' reward/effort. The effort levels were further calibrated to each individual during a practice session inside the scanner. During the practice, participants were presented with the effort challenge and encouraged to correctly complete all numbers as fast as they could. Calibration was based on the fastest trial out of 40 without errors (or until a sequence with all correct answers was achieved). The calibration individually adjusted the effort levels. Low, medium and hard effort corresponded to 20%, 40%, and 60% of the maximum completion speed, respectively. The effort levels were reduced from the previous version (Chapter 2) to increase success rates. Before the task commenced, participants had the opportunity to try out all effort levels. A rejected offer trial received the feedback: 'You passed'; a missed trial: 'Respond faster!'; an accepted and skipped trial: 'No response required'; an accepted and correct trial: '+ [reward level]'; an accepted and failed trial (greater than one error and/or time ran out): '+0'.

Participants completed six blocks of the task in the scanner with 54 condition trials (six trials per effort x reward combination) and six null event trials (fixation cross for eight seconds) per block, and also had the opportunity to rest between each block. Trial types (reward x effort combination) were presented in a random order with each block. Each block lasted around 12 minutes, resulting in a 1.2-hour task administration.

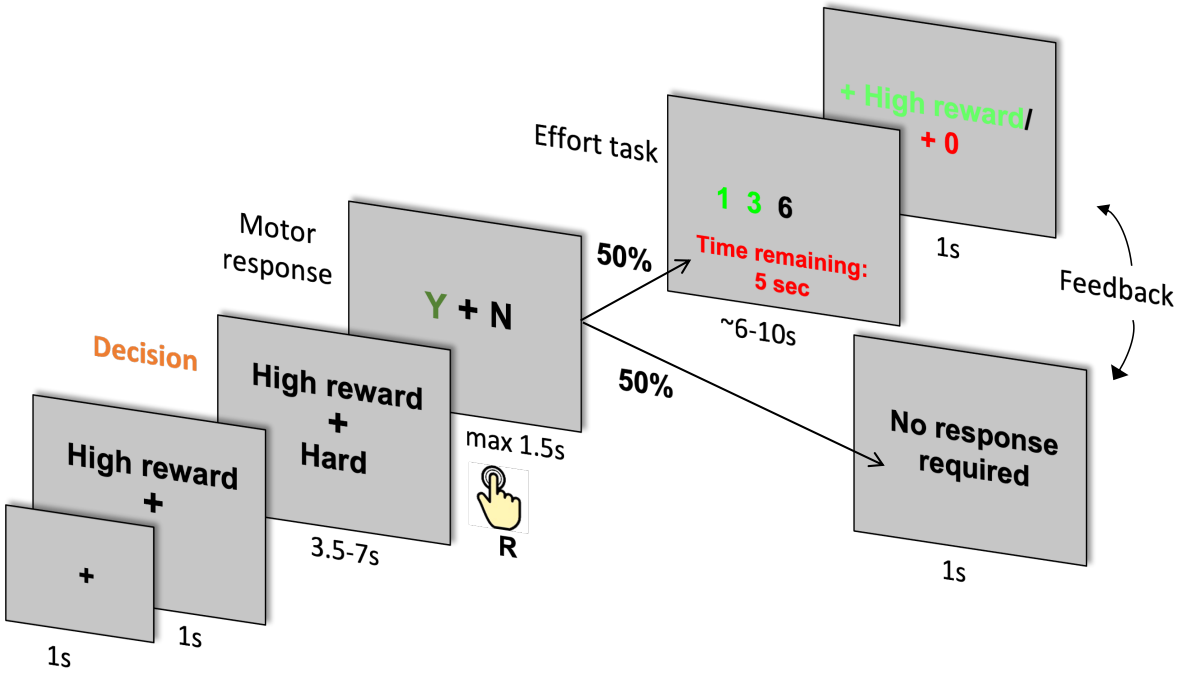

Figure 3.1 Cognitive effort task. On each trial, participants were presented with the amount of reward available (or effort needed to exert), and then additionally the amount of effort needed to exert (or reward available) to win points. The decision phase, when both reward and effort were presented, were of main interest. Participants were free to accept (Y) or reject (N) an offer. Half of the time that participants accepted an offer, they had to complete the effort challenge, which involved correctly categorising ten digits in a sequence as odd or even under time pressure. Effort was manipulated by allowing less time for the categorisation on higher effort levels.

3.3.2.2 Behavioural analyses

A within-subjects ANOVA with factors reward (low, medium, high) and effort (low, medium, high) was performed on the probability to accept an offer. Success rates across reward and effort levels were examined in the same way. Data were processed in Matlab (R2019b) and analysed in SPSS (v28, IBM Corp, Armonk, NY). Greenhouse-Geisser corrected values of degrees of freedom are reported throughout for repeated-measures ANOVAs if sphericity assumptions were violated. For all analyses, $p<0.05$ (two-tailed) was considered statistically significant.

3.3.3 Simultaneous EEG-fMRI recording set-up

Conducting simultaneous EEG-fMRI recording is technically challenging, especially for obtaining high quality EEG data. Extra care was taken to optimise the experimental set-up for high-quality EEG recordings and safety. This included keeping the EEG amplifier just outside and behind the MRI bore, preventing any looping of the EEG electrode bundle, and keeping cables outside the MRI bore to the greatest extent possible and exposing them to as few vibrations as possible by placing sandbags on top of the amplifier. Lights and ventilation were turned off for the duration of the scan.

Five individuals rejected fewer than nine (out of 324) trials. These individuals were therefore not included in the EEG and fMRI analyses (final N=17) since they were apparently insensitive to the effort and reward levels.

3.3.4 EEG data

3.3.4.1 Recordings

Continuous EEG data were acquired during simultaneous fMRI acquisition using MR-compatible EEG equipment (BrainProducts GmbH, Munich, Germany): a 32-channel customised BrainCap-MR and a BrainAmp-MR DC-amplifier. EEG was recorded with a sampling rate of 5kHz. The recording reference was located at Fz, and the ground electrode at Fpz. The scalp electrodes covered the 10-20-system with the following electrodes: Fp1/2, AFz, Fz, F7/8, F3/4, FC4/5, FC1/2, T7/8, C3/4, Cz, CP1/2, TP9/10, P3/4, Pz, P7/8, POz, O1/2, left/right EOG. An ECG electrode was used for ballistocardiogram (BCG; see section 3.3.4.2) artifact removal. EOG electrodes were placed 1cm below and lateral of the outer corner of the eye. To obtain optimal gradient artifact (GA) removal, the EEG clock was synchronised with the MRI scanner clock (Syncbox, Brain Products, Germany) and the fMRI slice repetition time (TR) was a multiple of the EEG clock period (EEG clock period is 200µsec) (Mullinger et al., 2013). Ground and reference impedances were kept below 10kΩ, with EOGs and ECG below 50kΩ and all other electrodes below 20kΩ. MRI slice triggers were collected to enable MR gradient artifact removal during preprocessing.

3.3.4.2 Preprocessing

EEG preprocessing was conducted using EEGLAB (version 2021.1) (Delorme & Makeig, 2004) in MATLAB (version R2019a). EEG data quality is severely compromised when acquired in an MR environment, obscuring the EEG signal, requiring several additional steps to preprocess the EEG data. The main artifacts include: 1) the GA, originating from the rapid switching of magnetic field gradients, inducing a current in EEG channels several hundred times greater than the neural activity (Allen et al., 2000); and 2) BCG artifacts related to cardiac-induced motion which can induce currents greater than the EEG signal and also at the same frequency as neural activity (Debener et al., 2007). Extensive exploration of several different open-source algorithms and toolboxes was conducted to optimize the obtained EEG data by retaining as much of the neural activity as possible while reducing artifacts as much as possible.

GA removal was explored using both a traditional sliding average template (AAS) (Allen et al., 2000) and a principal components analysis (PCA) method (default settings in AMRI toolbox version 1.1) (Liu et al., 2012). Based on inspecting the power spectral density of the data, it was determined that the AAS method over-corrects more than the PCA method under-corrects. To retain as much of the neural activity as possible, the PCA method was chosen for GA removal. For BCG artefact removal, the PCA method again outperformed and was chosen (using default settings in AMRI toolbox). Following GA but prior to BCG artifact removal, the data were downsampled to 250Hz and automatic heartbeat detection was applied to facilitate BCG artifact removal (AMRI toolbox). These were visually inspected, and poor automatic heartbeat detection was remedied manually. Following these artifact removals, a Butterworth, zero phase-shift, noncausal bandpass filter (24dB/octave roll off) was used between 0.1 and 20Hz based on recommendations for the P3 wave (Luck, 2014). The GA harmonics were removed with a 1Hz band rejection filter (Mayeli et al., 2021). Eye artifacts and any residual BCG artifacts were removed using independent components analysis (ICA) with the amica toolbox on the NeuroScience Gateway portal www.nsgportal.org (Hsu et al., 2018; Palmer et al., 2008). Bad channels were removed prior to ICA and interpolated following ICA. The data were then re-

referenced to the average of the TP9/10 channels (approximate mastoid location) and the online recording channel (FCz) was reinstated. Finally, the data were segmented into stimulus-locked epochs to the onset of the decision phase (-200ms to 800ms) and baseline-corrected (-200ms). Any trials missing a response were removed (mean trials=7.87, SD=8.01), and any trials with amplitudes greater than $\pm$ 100μV on any channels were removed (mean trials=8.30, SD=9.45).

3.3.4.3 Analyses

To identify the N2 and P3 and determine the optimal time-window to analyse over, a collapsed localizer over all trials during the decision phase and over the mean of the anterior channels (Fz, FCz, FC1/2, Cz) for the N2 and posterior channels (Pz, POz, P3/P4, CP1/2) for the P3 was used. This allows selecting a time-window that is orthogonal to the conditions that will be analysed and thus minimises window selection biases that may increase the probability of type I errors (Luck, 2014). No N2 component was observed in the anterior channels, thus this component was not examined. A P3 component was evident in the posterior channels but peaking earlier (between 220-280ms) than the classic P3 (i.e., P3b which is usually observed between 300-700ms; Figure 3.2). All main analyses therefore focused on the mean amplitude between 220-280ms. These included the effect of: 1) reward on accepted trials, and 2) effort on accepted trials. For these analyses, three contrasts (high minus low, high minus medium, and medium minus low) were explored at every *a priori* defined posterior channel (Pz, POz, P3/P4, CP1/2). These contrasts were conducted with a repeated-measures, two-tailed permutation test based on the tmax statistic (Blair & Karniski, 1993) with a family-wise alpha level of 0.05, which allows for correcting the large number of comparisons, using the Mass Univariate ERP Toolbox (Groppe et al., 2011). Prior to the permutation tests, the data were downsampled to 125Hz.

To explore whether any other timepoints may be involved in either effort or reward signalling, time points between 200 and 780ms at all 28 scalp electrodes were tested. It was considered unlikely that higher cognitive computations occur earlier than 200ms, which typically only

reflect early visual processes (Woodman, 2010). This was again performed using mass univariate analyses with tmax permutation-based tests, controlling the family-wise error (FWE) rate at alpha=0.05.

To ensure that the EEG data were of sufficient quality, a number of checks were implemented. Both motor responses and visual ERPs should be evident in the data. To examine motor-evoked ERPs, the data were locked to the onset of each participant's yes/no motor response and examined over the C3 and C4 channels (averaged over all trials). A negative motor-related potential should be evident around 20ms post-response and show a lateralised negative scalp topography over left motor cortex in right-handed individuals (Melnik et al., 2017). For the visual check, a grand-average ERP (all trials) was generated over O1 and O2 channels, locked to the presentation of the first part of the offer. The ERP was inspected for a visual N1/N70 peak (negative over visual cortex) (Luck, 2014).

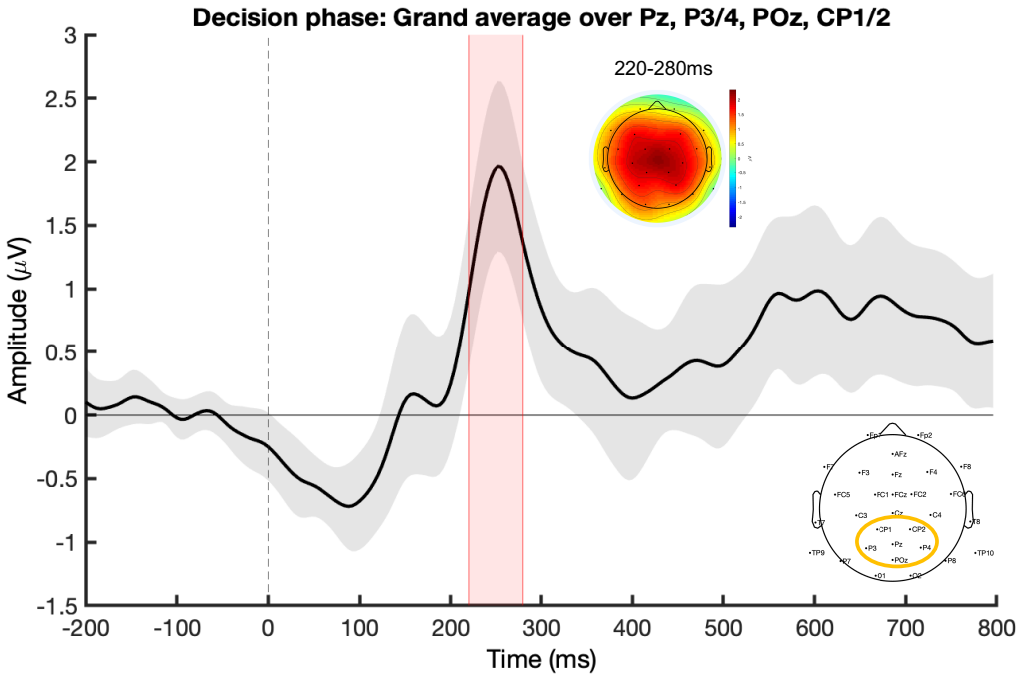

Figure 3.2 Collapsed EEG localizer. Trials across experimental conditions and posterior channels were used to identify the timing of an ERP component of interest for analysis at the onset of the decision phase. This approach is preferred in situations where prior research cannot inform the current study analysis parameters, as is the case in the current study. It further minimizes window selection biases and thus probability of type I errors. The shaded red area represents the time window used for the main analyses and the shaded grey area represents the 95% confidence interval.

3.3.5 fMRI data

3.3.5.1 Recordings

fMRI data were acquired using a 1.5T Siemens Avanto MRI scanner (Birkbeck-UCL Centre for Neuroimaging) with a 32-channel head coil. An echo planar imaging (EPI) sequence with 40 slices per volume, slice thickness of 2mm (1mm gap, 50% distance factor), slice TR of 85ms, transversal orientation, five dummy scans, an echo time (TE) of 50ms, a field of view (FOV) of 204 mm, and a flip angle of 80 degrees was used. EPI images were acquired in ascending order with a 3x3x2mm voxel size. Prior to acquisition of functional images, T1-weighted MPRAGE images with 1mm isotropic anatomical scans were acquired (sagittal orientation, 2730ms TR, 3.57ms TE, 7 degrees flip angle). A fieldmap was additionally acquired for each participant.

3.3.5.2 Preprocessing

Preprocessing of fMRI data was conducted using SPM12 (Wellcome Trust Centre for NeuroImaging, UCL, London, UK) in MATLAB (version R2017b). Slice-time correction was applied to all data to minimize sampling differences and temporally align the data. After discarding the first five scans, scans were realigned to the sixth volume. Scan-to-scan movements greater than 1.5mm (half voxel size) or rotations greater than 1 degree were manually inspected. If artefacts were observed, these images were removed and replaced using interpolation (with slice-time correction and motion correction repeated for these scans). Scans were then co-registered to each subject's anatomical scan and normalised to Montreal Neurological Institute (MNI) space. The normalised scans were then smoothed using a default Gaussian kernel of 8mm full-width at half maximum (FWHM).

3.3.5.3 Analyses

A whole-brain general linear model (GLM) analysis was conducted for accepted trials at the onset of the decision phase. The first-level analysis included regressors of reward and effort levels with a 1 s duration. Effort was modelled with a linear and quadratic parametric modulator, and reward with a linear parametric modulator (as some participants only accepted two reward levels) in the same model. Additional regressors of no interest included a parametric modulator on the feedback phase (loss and low, medium, high reward), a regressor for the motor response, the effort challenge (modelled with its duration), feedback when skipped, feedback when rejected, missed trials (duration of trial), and rejected offers (1 s duration). Serial orthogonalization in SPM was turned off and all parametric regressors were mean-centred. In addition, six movement parameters were included as nuisance regressors and null regressors were included to account for any interpolated scans during preprocessing. The second-level random-effects analysis was conducted with an initial cluster-forming threshold of p=0.001 and whole-brain FWE cluster-level correction of p=0.05, with one-sample t-tests for positive/negative reward and effort modulators. A second, otherwise identical model, additionally including a cost-benefit weighing parametric regressor (p(yes)-0.5) was conducted

(Bonnelle et al., 2016). However, due to the pattern of choices for some participants in several or all runs, this regressor was not estimable and thus this model was not considered further.

In addition to the whole-brain analysis, a region-of-interest (ROI) analysis was conducted to examine whether the ACC was involved in cognitive effort computations, since this region has shown to be of particular importance during effort cost computations (Husain & Roiser, 2018). The ACC region was identified through the Neurosynth database (www.neurosynth.org) with the keyword 'effort' and striatum and vmPFC was identified with the keyword 'reward'. A small volume correction with a 6mm radius sphere around the following MNI coordinates was applied for the ACC: x=0, y=14, z=46, left ventral striatum: x=-12, y=8, z=-8, right ventral striatum: x=12, y=10, z=-8, and vmPFC: x=2, y=58, z=-8:

3.3.6 EEG-informed fMRI

To better understand the origin of the identified ERP peak in the 220-280ms time window, single-trial mean amplitudes over this time-window were entered as a parametric modulator at the time of the decision in the first level GLM for each individual. Additional regressors included a parametric modulator of the feedback phase (loss, low, medium, high reward), regressors for the motor response, effort challenge, feedback of skipped trials, feedback of rejected trials, missed trials, rejected offers, and EEG artifact removed trials. The same threshold and correction for multiple comparison were applied in the second-level analysis as above.

3.4 Results

3.4.1 Behavioural results

3.4.1.1 Acceptance rates

As expected, participants' choices were significantly modulated by reward ($F_{(1.16,24.38)}$=45.48, p<0.001, η_p^2=0.68; Figure 3.3a), and effort ($F_{(1.18,\ 24.78)}$=19.37, p<0.001, η_p^2=0.48; Figure 3.3a). There was also a significant interaction ($F_{(2.27,47.67)}$=6.96, p=0.002, η_p^2=0.25), such that reward was discounted by effort to a greater extent at lower levels (Figure 3.3b).

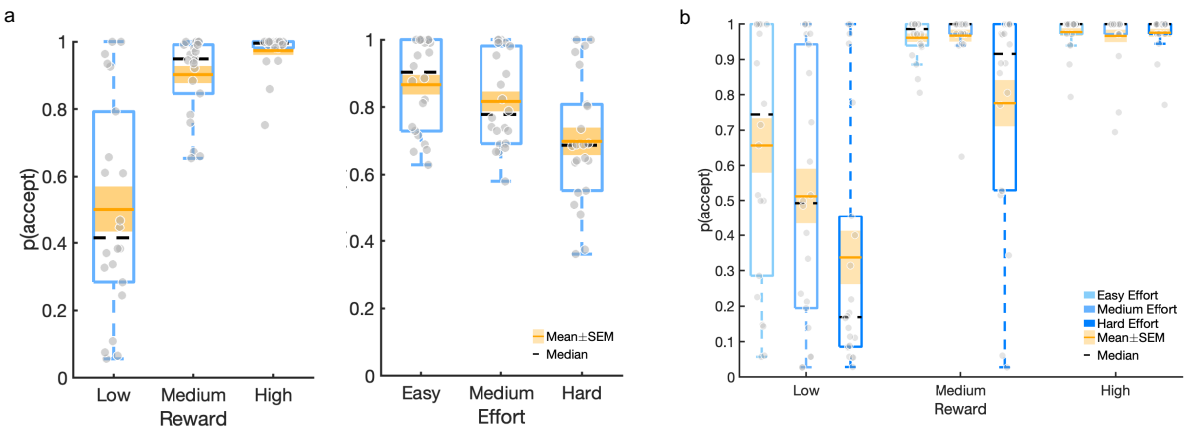

Figure 3.3 Acceptance rates. The probability to accept an offer increased with increasing reward levels and decreased with increasing effort levels (a). Acceptance rates also varied as a function of both effort and reward (b).

As a sensitivity analysis, we examined if the order of information (effort or reward presented first) influenced decisions. No significant order effects were observed (all p>0.17).

3.4.1.2 Task manipulation checks

Success rates. Success rates were uniformly high (Figure 3.4a). Importantly, there was no significant reward-by-effort interaction on success rates ($F_{(1.67,28.43)}$=1.10, p=0.34, η_p^2=0.06; N=18 as some participants did not accept at least one trial in each of the effort-reward combinations). There was no significant main effect of reward on success rates ($F_{(1.23,20.84)}$=2.31, p=0.14, η_p^2=0.12). However, a significant main effect of effort on success rates was observed ($F_{(1.29,21.90)}$=7.63, p=0.008, η_p^2=0.34). This was driven by lower success rates on the high compared with both medium (p=0.02) and low effort trials (p=0.01; Figure 3.4a). However, no significant correlations were found between overall accept and overall success rates (r=0.14, p=0.53), or between effort sensitivity (linear contrast of effort levels on acceptance rates) and the corresponding linear contrast on success rates (r=0.27, p=0.23; Figure 3.4b). This suggests that, even though participants performed slightly more poorly on the high effort trials, it was apparently not sufficiently substantial to impact their decision making.

Completion times. As expected, participants were faster to complete the effort task with increasing effort levels ($F_{(1.35,28.39)}$=6.38, p=0.01, η_p^2=0.23; low>medium: p=0.04; low>high: p=0.01; med>high: p=0.04; Figure 3.4c), suggesting that the effort manipulation was successful as participants modulated their behaviour according to the time limit. We further explored whether the number of switches also impacted performance. The time to complete the effort task increased with the number of odd/even switches on a given effort challenge trial ($F_{(2.71, 48.81)}$=8.25, p<0.001 η_p^2=0.31; N=19 as not all participants experienced every number of odd/even switches; Figure 3.4d). Figure 3.4e shows how many trials for each given number of odd/even switches on a trial per effort level. The data suggest that, although the number of switches also had an impact on how effortful the task was, the occurrence of each level of switches were roughly similar across effort levels. Thus, although we did not explicitly manipulate this aspect of the effort challenge design, it was fairly constant between effort levels and unlikely to have impacted choices since participants would not know in advance how many switches were available on a given trial.

Possible fatigue effects. To examine possible fatigue effects, a repeated-measures ANOVA with block (six blocks) and effort (low, medium, high) was performed on the probability to accept an offer, as well as on success rates. There was no significant interaction between block and effort ($F_{(4.24,88.96)}$=1.02, p=0.41, η_p^2=0.05), or a main effect of block ($F_{(1.91,40.08)}$=0.37, p=0.69, η_p^2=0.02) on the probability to accept an offer. There was no significant block-by-effort interaction on success rates either ($F_{(4.98,104.56)}$=1.17, p=0.33, η_p^2=0.05), but there was a significant main effect of block on success rates ($F_{(2.66,55.79)}$=2.91, p=0.048, η_p^2=0.12). This was driven by lower success rates overall on the last block (M=91.9%, SEM=2%) compared with the second (M=97.3%, SEM=0.7%; p=0.02), third (M=96.9%, SEM=0.08%; p=0.02) and fifth (M=95.9%, SEM=0.9%; p=0.03) blocks. These results indicate that fatigue effects were minimal, and largely confined to the last block.

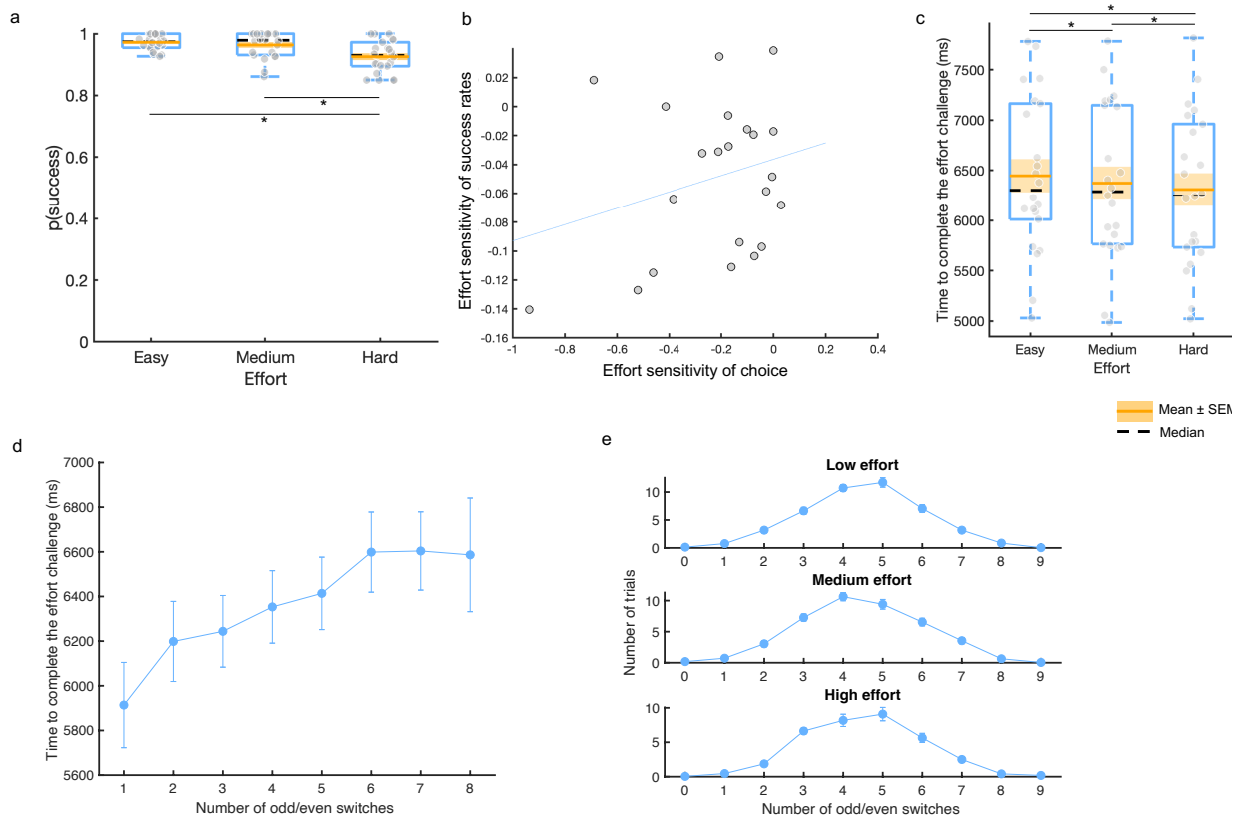

Figure 3.4 Manipulation checks. Boxplots of the probability to succeed on the effort challenge show that success rates were slightly lower on the hard effort condition (a) but effort sensitivity (linear contrasts of effort levels) to accept/reject an offer did not significantly correlate with effort sensitivity in terms of success rates (r=0.27, *p*=0.23; b). The time to complete the cognitive effort challenge decreased with increasing effort levels, in line with the effort manipulation (c). The time to complete the cognitive effort challenge further increased with the number of odd/even switches on a given challenge (d), but the distributions of odd/even switches were similar across all effort levels (e). Error bars reflect standard errors of the mean. *p<0.05.

3.4.2 EEG results

The linear contrast of effort (high minus low effort) survived FWE correction only at the P3 electrode (p=0.028; note that this ERP is coincidentally also termed P3). High effort had a greater mean amplitude between 220-280ms compared with low effort at the P3 electrode (Figure 3.5). All other tests of effort and reward during the decision to accept were non-significant at the corrected threshold level (p_{FWE}>0.20).

All participants had greater than 30 trials in each condition effort/reward level, which is the minimum recommended trials for analysing the P3 component (Luck, 2014), except for 4

individuals who accepted fewer than 11 trials in the low reward condition. The reward analysis was therefore repeated without these individuals as a sensitivity analysis. No reward conditions were significantly different from each other in this sub-analysis either (p_{FWE}>0.05).

To explore whether any other timepoints and electrodes might be affected by reward or effort, all time points between 200 and 780ms were examined. However, only the high versus low effort effect at 276ms at the P3 electrode was significant (reflecting the effect identified above). No other effects were significant when controlling the FWE rate at p<0.05.

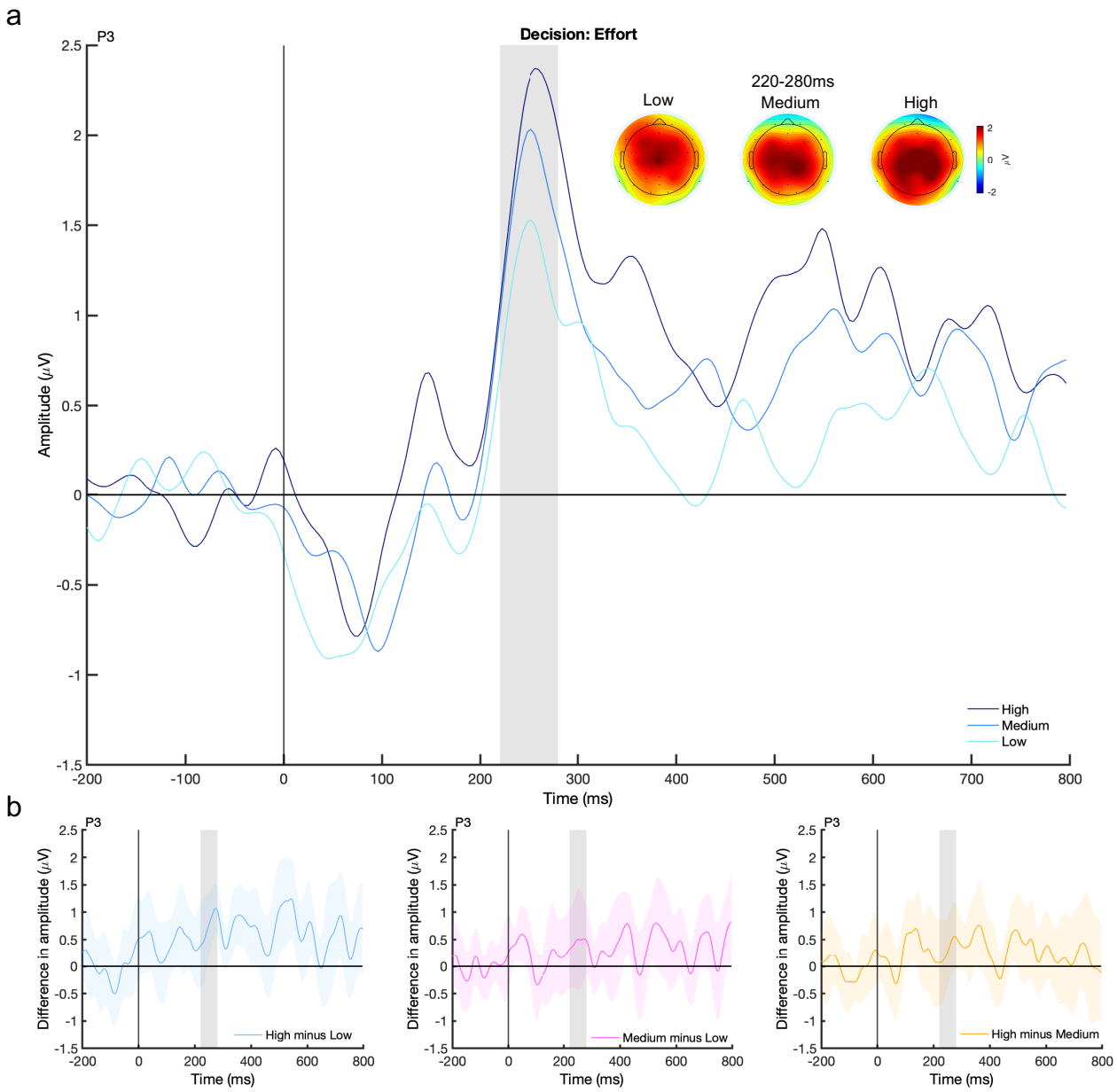

Figure 3.5 P3-like ERP modulated by effort on accepted trials at the time of the decision screen, at the P3 electrode. The top figure (a) shows the ERP for low, medium, and high effort, which was analysed in the shaded time window (220-280ms). Scalp topographies at the mean time window of 220-280ms are shown in the inset for each effort condition. Bottom figures (b) show the difference amplitude for each contrast. High effort showed a significantly greater mean amplitude of the shaded area compared with the low effort condition. Shaded regions around the difference waves indicate 95% confidence intervals.

3.4.2.1 EEG checks

Both visual (Figure 3.6a) and motor response (Figure 3.6b) ERPs were evident in the EEG data, suggesting that the EEG data were of good quality.

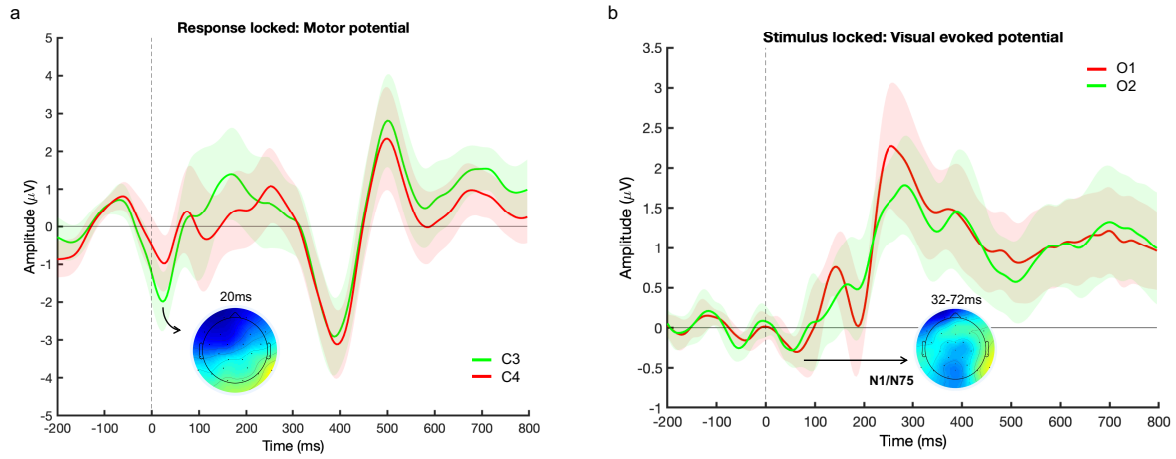

Figure 3.6 EEG data checks. The left plot shows the waveform from electrodes C3 and C4 at the onset of the choice (a). A motor potential is evident around 20ms after a response was made, showing greater activity over the left motor cortex, as expected for a cohort who are right-handed. The right plot shows waveforms over occipital channels (O1, O2) stimulus-locked to the first piece of information (reward or effort level), showing a negative peak around 70ms corresponding to the N1/N75 component (b). Shaded areas represent 95% confidence intervals.

3.4.3 fMRI results

3.4.3.1 fMRI: ROI analyses

No significant striatal or vmPFC clusters were identified for either the linear reward contrast or the linear/quadratic effort contrast. Significant ACC activation was however evident with a negative quadratic effort effect (MNI peak: -3, 14, 47; BA 24; small volume correction $t(16)=3.79$, k=8, $p_{FWE}=0.016$; Figure 3.7). This was driven by lowest activation in the low-effort condition, intermediate activation in the high-effort condition, and highest activation in the medium-effort condition.

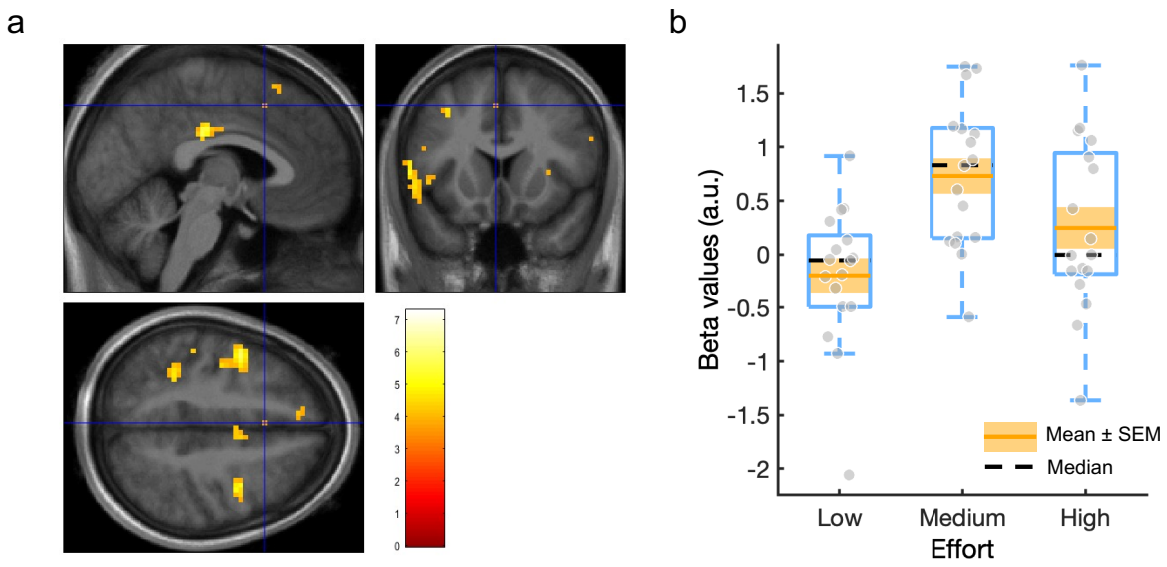

Figure 3.7 Effect of parametric negative quadratic effort modulation on ACC ROI activation. Effort-related activation in the *a priori* defined anterior cingulate cortex (ACC) region on accepted trials during the decision phase, identified using a cluster-forming threshold of $p<0.001$ and voxel-level family-wise error corrected within the region of interest at $p<0.05$.

3.4.3.2 fMRI: whole-brain analyses

A network of regions, including vlPFC, dlPFC, cingulate cortex, insula, and precentral gyrus encoded negative quadratic effects of accepted effort levels at the decision phase onset (Table 3.1).

In contrast, no regions emerged for the linear reward modulation of accepted trials at the time of the decision at a FWE-corrected cluster level. At a more lenient, exploratory, threshold (initial $p=0.01$, $p_{FWE}=0.05$ cluster corrected), only the precuneus and posterior cingulate cortex (PCC) showed significant effects with increasing reward levels (Table 3.1, Figure 3.8). There were no significant activations with decreasing reward levels, even at the more liberal initial threshold.

To better understand the quadratic effect of the effort results, the medium and high effort levels from each effort cluster (Table 3.1) were contrasted to examine whether they were different as a sensitivity analysis. The medium effort level was significantly lower than the high

effort level across all effort clusters, including the ACC ROI analysis (all p<0.005), consistent with a negative quadratic relationship with increasing effort levels, and not a step-wise effect relative to the lowest effort level.

Label	Coordinates for peak voxel			Size (voxels)	Peak *t*(16)	Cluster p_{FWE}
	x	y	z			
Neural activation with negative quadratic effort						
Left paracentral lobule/ precentral gyrus (BA 6)	-12	-7	56	222	7.29	<0.001
Right inferior temporal gyrus/ inferior occipital gyrus	51	-73	-4	69	7.05	0.004
Right anterior prefrontal cortex	30	47	11	48	6.60	0.023
Posterior cingulate cortex (BA23)/ middle cingulate cortex	0	-25	29	41	6.52	0.043
Right vlPFC/insula	39	23	2	58	6.27	0.010
Left middle temporal cortex (BA 21)	-57	-40	2	60	5.64	0.008
Left vlPFC	-57	11	11	150	5.60	<0.001
Left dlPFC/ anterior prefrontal cortex	-42	35	20	110	5.16	<0.001
Right middle frontal gyrus/ precentral gyrus (BA6)/ inferior frontal gyrus triangular part	36	-1	47	46	5.06	0.027
Neural activation with increasing reward						
Precuneus/posterior cingulate	-9	-73	50	437	6.36	<0.001*

Table 3.1 Whole-brain fMRI analysis of accepted trials during the decision phase. All clusters were corrected for multiple comparisons with a cluster-forming threshold of $p<0.001$ (uncorrected) and family-wise error (FWE) cluster correction at $p<0.05$. MNI coordinates are presented. Areas of activation were identified with a brain atlas (Mai et al., 2015). vlPFC: ventrolateral prefrontal cortex; dlPFC: dorsolateral prefrontal cortex. *No clusters for the reward modulator reached cluster-level FWE-correction when using a cluster-forming threshold of $p<0.001$ (uncorrected). The listed effect is present at a more liberal cluster-forming threshold of $p<0.01$ (uncorrected) and $p_{FWE}<0.05$ (original $p_{FWE}=0.158$ with cluster-forming threshold $p=0.001$).

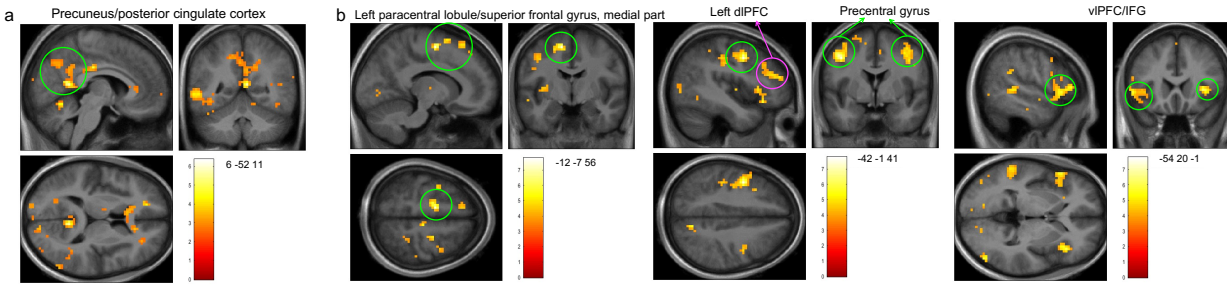

Figure 3.8 Effect of reward and effort on whole-brain activation. Whole-brain activation to parametric positive linear reward levels (a) and negative quadratic effort levels (b) on accepted trials at the decision-phase. All clusters are significant at a cluster-forming threshold of $p<0.001$ and family-wise error (FWE) cluster corrected at $p<0.05$, except the reward cluster which is only evident at a more liberal cluster-forming threshold of $p<0.01$ ($p_{FWE}<0.05$ cluster corrected). dlPFC: dorsolateral prefrontal cortex; vlPFC: ventrolateral prefrontal cortex; IFG: inferior frontal gyrus. Colour bars indicate t-values and x, y, z, coordinates are in MNI space.

3.4.4 EEG-informed fMRI results

No significant clusters were identified in the EEG-informed fMRI analysis using a cluster-forming threshold of $p<0.001$ and $p_{FWE}<0.05$ cluster-correction, or even when using a more lenient uncorrected initial threshold of $p<0.01$.

3.5 Discussion

The goal of this study was to characterise the spatiotemporal dynamics of motivation to exert cognitive effort. The main aims were to establish the spatiotemporal dynamics of reward benefits, and separately, effort costs, to understand how these may influence choices. This may help clarify the neural mechanisms underlying difficulties in motivation, as observed in anhedonia.

At a behavioural level, this task showed good face validity: reward motivated task engagement while effort decreased motivation to exert effort, as expected and in line with previous studies (Husain & Roiser, 2018). Importantly, success rates were uniformly high, suggesting that decisions were not influenced by how achievable the effort levels were. This is important, as otherwise decisions can be confounded by probability discounting, although this has not often been examined in effort paradigms. Similarly, decisions might also be confounded by the time to complete an effort challenge, as a more effortful challenge usually takes longer to complete leading to temporal discounting (Klein-Flügge et al., 2015). This is relatively easy to control for in physical effort paradigms, but harder to achieve for cognitive effort. Indeed, it is mostly not controlled for in current cognitive effort paradigms (Apps et al., 2015; Chong et al., 2017; Westbrook et al., 2013). In the current task, the number of digits to complete was the same for each effort level to avoid this confound. In addition, very minor fatigue effects were observed over six blocks; this is important because fatigue, which is conceptually related to anhedonia, also impacts motivation (Müller & Apps, 2019). Crucially, we were able to calibrate the effort challenge to each individual, which provides confidence that decisions are not related to individual differences in ability to complete the cognitive challenge per se. This is particularly important in clinical case-control studies, as patients may often experience cognitive impairment which could confound the results. Finally, by adopting a single-action decision to accept or reject offers, versus binary choices (low effort-low reward or high effort-high reward), this task might more closely mimic real-life decisions (Bonnelle et al., 2015; Pessiglione et al., 2018).

At a neural level, we observed that ACC activation scaled with anticipated effort during the decision phase, consistent with the study hypotheses, albeit in a negative quadratic manner. Sensitivity to physical effort has previously shown to depend on the ACC (Bonnelle et al., 2016; Klein-Flügge et al., 2016). This suggests that cognitive effort might recruit similar neural regions as physical effort, at least during option valuation. Both domain-general and domain-specific neural mechanisms have been identified for decisions involving physical and cognitive effort (Chong et al., 2017). However, these were only examined for the cost-benefit valuation (i.e., the integration of rewards and efforts), and thus it remains unclear whether sensitivity to physical or cognitive effort is processed in the same neural regions.

Surprisingly, ACC activation showed a negative quadratic relationship with increasing effort levels. The reason for this is not clear. On a physical effort version of this task, subjective valuation of effort is represented by both a linear and quadratic effort computational parameter (where a negative quadratic parameter indicates disproportionate increase in sensitivity to high effort levels) (Armbruster-Genç et al., 2022). Thus, it is possible that our results are related to this quadratic valuation of effort. This may indicate that cognitive effort is implemented in similar regions to physical effort, but that the computations may differ by effort domain. Future studies will need to clarify this by employing a computational approach. Alternatively, this ACC activation might reflect decision difficulty. Low and high effort trials might result in easier decisions (mostly accept and reject, respectively), than the medium effort level, which requires more deliberation. Indeed, the ACC has also been implicated in decision difficulty and conflict monitoring (Bonnelle et al., 2016; Westbrook & Braver, 2015). However, mean acceptance rates were high over all effort levels (over 70%) and the high effort level was closest to a mean acceptance rate of 50%, which would indicate that this level produced the most difficult decisions. Nevertheless, it is recognised that the ACC is involved in a plethora of processes (Ebitz & Hayden, 2016; Vassena et al., 2017), and thus future work is needed to establish its role in cognitive effort valuation. Finally, it is unlikely that this effect reflects differences in trial numbers as the number of accepted trials scaled linearly with effort levels.

Thus, the quadratic neural modulation of effort remains unclear but these results suggest a relationship with the effort manipulation. Nevertheless, this effect requires replication and future studies could clarify this using a computational model. Interestingly, a quadratic pattern corresponding to effort level was observed across all significant neural regions. Among others, these included frontal regions such as the dlPFC and vlPFC, and superior frontal gyrus; regions typically identified in higher-order cognitive processes, such as attention, inhibitory control and flexible cognition, as well as mental effort exertion (Friedman & Robbins, 2022; Nelson & Guyer, 2011; Ryman et al., 2019; Soutschek & Tobler, 2020).

We did not observe that evaluation of reward during the decision to accept an offer scaled significantly with activation in either the vmPFC or striatum, as previously reported for physical effort tasks (Pessiglione et al., 2018). Reward evaluations were related more to PCC activation, but only at a lenient threshold, in line with one previous physical effort study (Klein-Flügge et al., 2016). Although not included in our predictions, the PCC is often activated during reward processing, together with the striatum and vmPFC (Bartra et al., 2013). Moreover, previous studies only identified vmPFC activity in individuals whose choices were most strongly driven by reward, as measured by a computational model (Klein-Flügge et al., 2016). Future studies could therefore use a model to elucidate if this might also be the case in the present study. Importantly, however, no regions overlapped between reward and effort, suggesting that the identified neural regions activate in a relatively specific manner to different types of information.

Contrary to our hypotheses, we did not observe any classic N2 or P3 ERPs in frontal and posterior scalp electrodes. Although a P3-like ERP was observed in parietal channels, this did not scale with reward as hypothesised. Instead, a higher amplitude was observed with greater effort levels during the decision to accept. One previous study indicated that the amplitude of the P3, measured during anticipation of rewards on the MID task, increased with the willingness to accept high-effort/high-reward trials on the EEfRT (Zhang et al., 2017). However, unfortunately in that study EEG recording was not performed during EEfRT performance. Our

results suggest that perhaps this effect is driven by effort costs, rather than reward benefits. However, we did not detect correspondence between the activity of this P3-like component and any neural regions in our EEG-informed fMRI analysis. This might have occurred due to the poor signal-to-noise ratio inherent in single-trial EEG. Even though the EEG data were of sufficient data quality on average, this might not have been sufficient on a single-trial level and might need to be further optimised in an MRI environment. In addition, effort showed a linear relationship with this ERP, in contrast to the fMRI pattern, potentially reflecting different effort-related evaluation processes. However, in the absence of an identified neural generator, the P3-like ERP is difficult to interpret, and should be considered preliminary.

No N2 component was evident in frontal scalp channels. The reason behind this is not clear. Although we conducted a small pilot using only EEG, and did observe both N2 and P3 components in expected channel locations, some individuals did show an N2 fronto-central component in the current study (data not shown), suggesting that this task might not have consistently engaged the N2 component. Speculatively, this might be because the N2 component is mainly associated with executive functions, such as conflict monitoring and task difficulty, during the *execution* of such processes (Folstein & Van Petten, 2008), but might not be involved in the *decision* whether to engage or not in such processes.

This study had several limitations, the main one being the small sample size. This was intended to be a pilot study to identify neural markers of interest, but this meant that we were also unable to examine certain analyses, such as brain-behaviour correlations. In addition, we did not examine reaction times, which might be informative for understanding the timing of decisions. This was due to the task design: choice execution was separated from the offer phase in order to avoid any possible confounds from the motor-response or post-decisional factors, and thereby increase sensitivity for examining decision-related processes. Finally, it is possible that our choice to present reward/effort information separately before the decision screen unexpectedly affected on our ability to detect typical ERP markers. This design was chosen to ensure that each condition (reward or effort) was processed sufficiently so that it would be

possible to examine ERPs close to the onset of the offer screen, as ERPs are typically examined within the first couple of hundred milliseconds. Although our behavioural analysis indicated that decisions were not affected by the order of presentation, we did not examine if this might have influenced the neural data due to the low sample size in each condition (eight individuals were presented with the effort level first and nine individuals with reward first). Future studies should examine this possibility.

In summary, the current task addresses several shortcomings of previous paradigms and shows promise for examining willingness to exert cognitive effort. The neural mechanisms underlying decisions involving cognitive effort have remained largely unknown. The current study suggests that decisions to accept based on cognitive effort might be computed in regions previously identified as being involved in physical effort valuation, such as the ACC, and other regions involved in higher-order cognitive functions such as the dlPFC and vlPFC. A negative quadratic pattern was identified, with strongest activation for decisions involving medium effort levels. An ERP component around 200-300ms was associated with increasing effort linearly, but we were unable to demonstrate that this ERP corresponded to activation in the identified cognitive-effort-related regions. Overall, these results suggest that the motivation to exert cognitive effort elicits activation in a robust network concentrated on PFC regions with decisions about effort costs tentatively being most prominent around 200-300ms. Future, larger, studies are required to clarify the temporal dynamics of decisions involving cognitive effort in greater detail.

4 The effect of ketamine on fronto-striatal circuitry in depressed and healthy individuals: a resting-state fMRI study

4.1 Abstract

Ketamine improves motivation-related symptoms in MDD, but simultaneously elicits similar symptoms in healthy individuals, suggesting that it might have different effects in different populations. This study examined whether ketamine affects the brain's fronto-striatal system, which is known to drive motivational behaviour. It also assessed whether inflammatory mechanisms—which are known to influence neural and behavioural motivational processes—might underlie some of these changes. These questions were explored in the context of a double-blind, placebo-controlled, crossover trial of ketamine in 33 individuals with TRD and 25 healthy controls (HCs). Resting-state fMRI (rsfMRI) was acquired two days post-ketamine (final sample: TRD N=27, HC N=19) and post-placebo (final sample: TRD N=25, HC N=18) infusions and was used to probe fronto-striatal circuitry with striatal seed-based functional connectivity. Ketamine increased fronto-striatal functional connectivity in TRD participants towards levels observed in HCs while shifting the connectivity profile in HCs towards a state similar to TRD participants under placebo. Preliminary findings suggest that these effects were largely observed in the absence of inflammatory (C-reactive protein; CRP) changes, and were associated with both acute and sustained improvements in symptoms in the TRD group. Ketamine thus normalized fronto-striatal connectivity in TRD participants but disrupted it in HCs independently of inflammatory processes. These findings highlight the potential importance of reward circuitry in ketamine's mechanism of action, which may be particularly relevant for understanding ketamine-induced shifts in motivational symptoms.

4.2 Introduction

The precise neural mechanisms underlying ketamine's beneficial effects remain unknown. Unlike other antidepressants, ketamine is particularly effective in treating motivational dysfunction, such as anhedonia (Ballard et al., 2018; Lally et al., 2014; Lally et al., 2015). In a parallel line of research, ketamine has also been used to model symptoms of schizophrenia in HCs (Frohlich & Van Horn, 2014). Interestingly, some of those studies suggested that ketamine can transiently *induce* symptoms relating to impaired motivation in HCs (Driesen et al., 2013; Pollak et al., 2015; Stone et al., 2008; Thiebes et al., 2017). This echoes findings that ketamine moderately increased anhedonia and symptoms of difficulty in decision-making in HCs beyond its dissociative side effects (Nugent et al., 2019). While this prior work suggests that ketamine's effects may be mediated through changes in motivational processing, the neural circuit-level mechanisms underlying this are poorly understood.

A neural pathway of interest here is the brain's reward circuit, including striatum and ventral PFC (Haber, 2016). The striatum acts as an important hub in the brain's reward system and is thought to drive goal-directed behaviours through interplay with the PFC (Haber & Knutson, 2010; Marquand et al., 2017). For this reason, both theoretical and empirical accounts implicate the fronto-striatal circuit as a key driver of motivational behaviour. In depressed individuals, task-based fMRI studies have consistently identified abnormalities in the brain's reward system. Specifically, altered function has been observed in the OFC, dlPFC, and perigenual (pg) ACC, with striatal hypoactivation consistently implicated in MDD (Admon & Pizzagalli, 2015; Eshel & Roiser, 2010; Heller et al., 2009; Husain & Roiser, 2018; Price & Drevets, 2010, 2012). Lower fronto-striatal functional connectivity has also been associated with MDD and anhedonia during reward processing (Borsini et al., 2020; Heller et al., 2009; Rupprechter et al., 2020). Complementing and extending these findings, studies using rsfMRI—which is thought to reflect the intrinsic functional organization of neural circuits—reported that MDD is associated with altered functional connectivity between striatal and prefrontal regions (Furman et al., 2011; Gong et al., 2018; Hamilton et al., 2018; Kaiser et al., 2015; Marchand, 2010; Pan et al., 2017; Treadway & Pizzagalli, 2014). Furthermore, disrupted striatal and prefrontal function have been

associated with individual differences in reward-related processing (Felger et al., 2016; Greenberg et al., 2015; Sharma et al., 2017; Wang et al., 2016; Yang et al., 2017), suggesting that fronto-striatal circuitry plays an important role in the pathogenesis of motivational impairment.

Several inflammatory processes have recently been proposed to influence the function of this fronto-striatal circuit as well as motivational impairments in MDD (Cooper et al., 2018; Felger & Treadway, 2017; Miller & Raison, 2015). Elevated peripheral markers of inflammation—as measured by CRP—have been associated with depression (Chamberlain et al., 2019; Haapakoski et al., 2015; Miller et al., 2009) and with lower cortico-striatal functional connectivity (Felger et al., 2016; Yin et al., 2019). Experimentally-induced inflammation in animals and humans has also been shown to cause motivational impairments and reduce striatal function (Capuron et al., 2012; Dantzer et al., 2008; Eisenberger et al., 2010; Vichaya & Dantzer, 2018). Inflammation may mediate motivational symptoms by dampening dopamine activity within reward circuitry, resulting in disrupted fronto-striatal functional connectivity (Felger & Treadway, 2017). Inflammatory processes are therefore well-situated to influence neural circuits underlying motivational symptoms. Interestingly, ketamine may affect dopaminergic function through glutamatergic downstream effects (Belujon & Grace, 2014; Kokkinou et al., 2018) and may also influence inflammatory processes (De Kock et al., 2013; Yang et al., 2015).

Although these studies lend credence to the hypothesis that fronto-striatal circuitry is important in ketamine's mechanism of action, this has never been directly tested. A secondary question is whether ketamine-induced fronto-striatal changes are mediated via inflammatory mechanisms. These questions were explored in the context of a double-blind, placebo-controlled, crossover trial of ketamine in individuals with TRD and HCs that used rsfMRI to probe fronto-striatal circuitry and CRP measures to quantify peripheral inflammation. Given that ketamine has opposite effects on motivational symptoms in individuals with TRD and HCs, ketamine's effects on reward circuitry and inflammation—two important neurobiological

mechanisms underlying motivational behaviours—may underlie these observations. Based on prior studies indicating lower functional connectivity in fronto-striatal circuitry in MDD, it was hypothesised that ketamine would increase fronto-striatal functional connectivity in TRD participants but decrease it in HCs, and that these effects would be associated with ketamine-induced changes in inflammatory response.

4.3 Methods

4.3.1 Participants

Data for 58 participants (25 HCs and 33 TRD participants) were drawn from a larger clinical trial (NCT00088699) (Evans et al., 2018; Nugent et al., 2019). All participants were evaluated using the Structured Clinical Interview for Axis 1 DSM-IV Disorders (SCID)-patient and nonpatient versions (NP) (First et al., 2002a, 2002b). All TRD participants met criteria for recurrent MDD without psychotic features, had a Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) score $\geq$20 at screening and before each infusion, had not responded to at least one adequate antidepressant trial during their current episode, and had a current episode that lasted for at least four weeks. Before testing, all TRD participants were medication-free for at least two weeks (five weeks for fluoxetine, three weeks for aripiprazole). HCs had no family history of Axis I disorders in first-degree relatives as determined by the SCID-NP. All participants were between 18-65 years of age and deemed to be in good physical health with no unstable medical problems, as determined by medical history, physical examination, blood labs, chest x-ray, electrocardiogram, toxicology, and urinalysis. Additional exclusion criteria included a current or past (past 3 months for patients, and lifetime for HCs) comorbid substance abuse or dependence (not including nicotine/caffeine) and any MRI contradictions. Female participants could additionally not be pregnant or nursing throughout their participation. All participants were admitted to an inpatient psychiatric unit at the NIMH during the study and provided written informed consent. The study was approved by the NIH Combined Central Nervous System IRB.

4.3.2 Study procedures

Participants were randomized to receive either a single intravenous infusion of subanaesthetic-dose ketamine hydrochloride (0.5 mg/kg) or placebo (0.9% saline solution) during the first session and the alternative treatment in the second session, conducted two weeks later (Figure 4.1). rsfMRI scans were obtained two days following each infusion. Ketamine and saline solutions were administered in identical syringes over 40 minutes via intravenous tubing in the forearms, and all subjects, researchers and clinicians were blind to the treatment assignment.

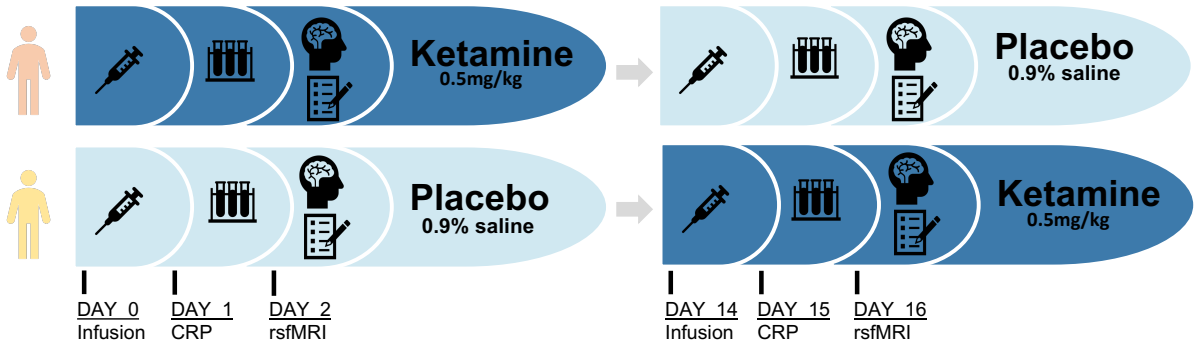

Figure 4.1 Study design. Participants were randomised to receive either a subanaesthetic dose of ketamine or a placebo on their first infusion and the alternative treatment on their second infusion, two weeks later. Inflammatory markers (C-reactive protein: CRP) were analysed one day post-infusions and resting-state fMRI (rsfMRI) two days post-infusions.

4.3.3 fMRI acquisition and preprocessing

Data acquisition and preprocessing have previously been reported and were identical to those described in Evans et al. (2018). Eight-minute rsfMRI scans (3.75x3.75x3.5mm resolution, 64x64 matrix, TR of 2.5s) were acquired on a 3T GE Healthcare MRI scanner (HDX; Milwaukee, WI) with an eight-channel coil. Participants were asked to close their eyes and relax but not fall asleep. rsfMRI scans were obtained two days following each infusion; given ketamine's short half-life (Clements, 1982), it had been fully metabolized by this time point, which allowed us to examine lasting neural effects not attributable to ketamine's immediate pharmacological effects. High-resolution structural images were obtained using a T1-weighted 3D fast spoiled gradient recalled echo sequence with an 8.8s TR, 3.4ms TE, 450ms inversion recovery time, 13

degrees flip angle, and with a 1mm isotropic resolution. Whole-brain rsfMRI images were obtained using a gradient recalled EPI sequence with a 90 degrees flip angle, 192 volumes, 45 slices per volume, 3.75x3.75x3.5mm resolution, 64x64 matrix, TR of 2.5s, TE of 25ms, anterior-posterior phase encoding direction and interleaved acquisition. In addition, cardiac and respiration traces were recorded during each scan using the GE photoplethysmograph and respiratory belt.

Preprocessing was performed in AFNI with the afni_proc script. This included despiking, slice-time correction, nuisance signal regression (motion: 12-parameter affine, registered to the third volume; physiological: slice-based, generated with McRetroTS), 6mm FWHM spatial smoothing, band-pass filtering (0.01-0.1Hz), alignment to the MNI 152 standard space, and motion censoring. Alignment to standard space was achieved by first aligning the structural image to the EPI with an affine transform using the LPC cost-function (align_epi_anat.py in AFNI). The anatomical image was non-linearly warped to the MNI 152 standard template and the EPI was transformed to standard space using the concatenated transformation matrices produced from the anatomical alignment steps. Image sequences were censored (i.e., removed) if there was movement greater than 0.2mm (Euclidean norm) per TR. If there were more than 15 censored time points per dataset, the dataset was excluded from further analysis. Motion (de-meaned and derivative) regressors were removed from the original time series simultaneously with band-pass filtering.

As reported previously (Evans et al., 2018), data were excluded for the following reasons: incomplete physiological data (six TRD individuals and four HCs); excessive motion (>0.2mm/TR; nine TRD, 11 HC); high correlation between the respiration volume trace and the average global signal, which increased correlations across the brain (three TRD, three HC); and an extreme outlier data point in the group x treatment interaction results (one HC, excluding this individual did not significantly alter any results).

4.3.4 Seed regions

In line with previous studies (Di Martino et al., 2008; Felger et al., 2016; Furman et al., 2011), four striatal seeds reflecting striatal functional subregions were chosen to assess fronto-striatal circuitry (3.5mm radius spheres). These included the ventral striatum (VS; ± 9, 9, -8), dorsal caudate (DC; ± 13, 15, 9), dorsal caudal putamen (DCP; ± 28, 1, 3), and ventral rostral putamen (VRP; ±20, 12, -3; see Figure 1). Left and right seeds were combined for analysis to increase signal-to-noise, as we expected that left and right seeds would show similar activity. For each participant, seed locations were visually inspected with reference to anatomical images to ensure appropriate positioning.

4.3.5 ROI control

The primary visual cortex (V1) was used as a control region for a sensitivity analysis examining whether the results were specific to the identified PFC regions or due to a global pattern. Left and right ROIs (3.5mm sphere radius per ROI) were collapsed for analysis (±8, -76, 10) (Yu et al., 2008).

4.3.6 Peripheral inflammatory markers

CRP levels were used to assess peripheral inflammation, which show high correspondence with central markers of inflammation (Felger et al., 2018). These were acquired 60 minutes prior to each infusion and at 230 minutes, Day 1, and Day 3 after each infusion. Only data from Day 1 were examined here as it was the timepoint closest to the scan and the infusion day and had the greatest number of available samples.

Blood samples were collected using vacutainer tubes with sodium heparin and centrifuged at 3000 rpm at 4°C for 10 minutes. Separated plasma samples were aliquoted and stored at -80°C until assay. Prior to processing, plasma samples were randomly allocated in the plates and blinded independently to minimize the impact of batch, treatment, or group effect in the sample. High-sensitivity CRP was quantified using the human CRP DuoSet ELISA kit (R & D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Plasma was

diluted 1:1000 with reagent diluent and carried out in duplicate, blind to clinical information. CRP standard solution was diluted to concentrations from 15.6 to 7500pg/ml to create the standard curve. After the addition of biotinylated detection antibody, streptavidin-HRP substrate, and stop solution (stepwise), plates were read at 450 nm with Synergy HTX Multi-Mode Reader (BioTek, Winooski, VT, USA). CRP concentrations were calculated based on the standard curve.

4.3.7 Symptom scales

MADRS and SHAPS ratings were acquired 60 minutes before each infusion and at 40, 80, 120, 230 minutes, and 1, 2, 3, 7, 10, and 11 days following each infusion. The SHAPS is a 14-item, self-administered psychometric scale (Snaith et al., 1995). Each item was scored between 1-4, resulting in a final score range between 14 and 56. For both scales, participants were asked to indicate how they felt since the last time the rating was administered. The primary symptom outcome was from Day 2, as this was the day of the rsfMRI scan. Secondary symptom outcomes were from Day 10, to explore if any ketamine-induced changes in fronto-striatal circuitry may have played a role in more sustained symptom improvements. For the correlations with the longer-term anti-anhedonic or antidepressant effects, psychometric data from Day 10 were chosen as this day had the greatest number of available samples.

4.3.8 Data analysis

Seed-to-whole-brain functional connectivity analyses were performed in AFNI (v.19.0.09) (Cox, 1996) and all other analyses were conducted in SPSS (v25, IBM Corp, Armonk, NY). For all non-neuroimaging analyses, statistical significance was assessed at $p<0.05$, two-tailed, without correction for multiple comparisons due to the exploratory nature of the study. No *a priori* power analysis was performed because the present study was a secondary analysis of a clinical trial (Nugent et al., 2019). However, conducting a retrospective sensitivity power analysis in G*Power (Faul et al., 2007) showed that we had 80% power to detect an effect size of 0.89 between groups with 25 patients and 18 HCs (two-tailed, alpha=0.05).

4.3.8.1 Functional connectivity

The final post-ketamine sample included 27 TRD participants and 19 HCs, and the final post-placebo sample included 25 TRD participants and 18 HCs. Functional connectivity Fisher transformed z-maps were generated at the subject-level using 3dNetCorr in AFNI (Taylor & Saad, 2013). Linear mixed-effects models were conducted (3dLME) (Chen et al., 2013) at the group level to assess the effect of treatment on each seed region-to-whole-brain functional connectivity map. Each model included: random effect of subject; within-subject factors of treatment (ketamine, placebo) and infusion order; and a between-subjects group factor (HC, TRD). Infusion order was retained if there were significant treatment interactions. The main purpose of this study was to examine the group-by-treatment interaction but all results are presented for completeness. An initial cluster-forming threshold of $p<0.005$ (uncorrected), with cluster-level FWE correction at $p<0.05$ was used to correct for multiple comparisons. Monte-Carlo simulation in AFNI (3dFWHMx, 3dClustSim) yielded a minimum cluster size of 46 voxels. Significant clusters—derived from the group-by-treatment whole-brain analyses—were used in correlational analyses with symptoms and CRP measures as described below.

For the V1 control analyses, linear mixed-effects models (random effect: subjects; fixed effects: group, treatment, and their interaction) were conducted to assess whether ketamine influenced striatal (VS, DC, DCP, VRP)-V1 functional connectivity.

4.3.8.2 Inflammatory markers (CRP)

Linear mixed-effects analyses (random effect: subjects; fixed effects: group, treatment, and their interaction) were conducted to assess the effect of ketamine on CRP levels. For this analysis, CRP measures were log-transformed to conform to assumptions of normality. CRP has previously been strongly positively associated with body mass index (BMI) (Chamberlain et al., 2019; Ridker et al., 2003; Zhao & Lv, 2013). To examine if this was the case in the current sample, BMI was correlated with both raw and log-transformed CRP levels at placebo and ketamine for both groups. An independent *t*-test was further used to examine whether there were any baseline differences in CRP levels (log-transformed) between groups (TRD N=30, HC

N=21). The -60 minute timepoint before the first infusion was used for the CRP data, as this most closely resembled approaches used in other cross-sectional studies investigating CRP levels between HCs and individuals with depression (Chamberlain et al., 2019).

Pearson correlation coefficients explored the relationship between change in CRP measures and ketamine-induced shifts in fronto-striatal functional connectivity. Participants were included if they had CRP and rsfMRI data for both post-infusion days (ketamine and placebo). Thirty-eight participants (TRD: 22, HC: 16) had usable CRP and rsfMRI data at both post-infusion timepoints. Changes in CRP levels (ketamine minus placebo; ΔCRP) were correlated with changes in functional connectivity (ketamine minus placebo; ΔFC) for each identified region from the seed-to-whole-brain functional connectivity result (i.e., the group-by-treatment interaction results). Correlations were conducted separately for each group. We also explored whether baseline CRP levels might moderate the change in fronto-striatal circuitry and anhedonia post-ketamine in individuals with TRD. The average of the log-transformed baseline CRP measures (-60 timepoint before both infusions) were correlated with change in SHAPS scores (ketamine minus placebo) as well as change in each identified striatal-frontal functional connectivity (ketamine minus placebo).

4.3.8.3 Symptom scales

A linear mixed effects model per group and symptom scale (MADRS, SHAPS) was used to examine the effect of ketamine versus placebo on symptoms. Each model included a random effect for participants along with fixed effects of time, treatment, and their interaction. Baseline scores on each infusion day (-60 minutes) was included as a covariate to correct for baseline symptom levels. Functional connectivity changes were correlated with ketamine's acute and longer-term anti-anhedonic or antidepressant effects in TRD. Differences in MADRS (ketamine minus placebo; ΔMADRS) and SHAPS (ketamine minus placebo; ΔSHAPS) scores on Day 2 (the rsfMRI scan day) and Day 10 were correlated with post-ketamine changes in fronto-striatal functional connectivity (ketamine minus placebo). Twenty-two TRD participants had MADRS scores at Day 2 after both infusions, and 12 TRD participants had SHAPS scores at Day 2

after both infusions. Nineteen TRD participants had MADRS scores at Day 10 after both infusions, and 12 had SHAPS scores at Day 10 after both infusions.

4.4 Results

4.4.1 Participant characteristics and psychometric scales

The patient group included significantly more Caucasian individuals than the healthy control group, with no other significant difference in demographic characteristics (Table 2.1).

	TRD (N=30) Mean (std. dev.)	**HC (N=21) Mean (std. dev.)**	***p*-value**
Age	36 (9.54)	34 (10.97)	0.55
Female	18 (60%)	14 (67%)	0.63
BMI (kg/m^2)	26.54 (5.66)	27.87 (4.16)	0.37
Caucasian (%)	25 (83%)	11 (52%)	0.02
Length of illness	20.80 (10.74) years	–	
Length of current episode	45.50 (73.20) months	–	
Number of failed antidepressant treatments	6.5 (3.66)	–	

Table 4.1 Characteristics for participants with at least one post-infusion (ketamine or placebo) scan included in the rsfMRI analyses. BMI: body mass index; rsfMRI: resting-state functional magnetic resonance imaging; TRD: treatment-resistant depression; HC: healthy control

As reported previously with this sample (Nugent et al., 2019), ketamine had a significant effect on both MADRS and SHAPS scores (Figure 4.2). In patients, ketamine significantly decreased MADRS scores (main effect of treatment: $F_{(1,480.65)}$=127.23, p<0.001), and this did not vary with time (treatment-by-time interaction: $F_{(9, 471.25)}$=1.18, p=0.31). Similarly, ketamine significantly decreased SHAPS scores in patients ($F_{(1,280.89)}$=52.80, p<0.001), with no significant interaction effect with time (treatment-by-time interaction: $F_{(9, 263.89)}$=0.85, p=0.57). There was a significant main effect of treatment on MADRS scores in healthy controls ($F_{(1,290.10)}$=33.45, p<0.001), with a temporary increase in depressive symptoms (treatment-by-time interaction: $F_{(9,282.97)}$=7.68, p<0.001). Similarly, ketamine significantly increased SHAPS scores in healthy controls ($F_{(1,219.883)}$=7.81, p=0.006; no significant interaction with time: $F_{(9,205.61)}$=1.00, p=0.44).

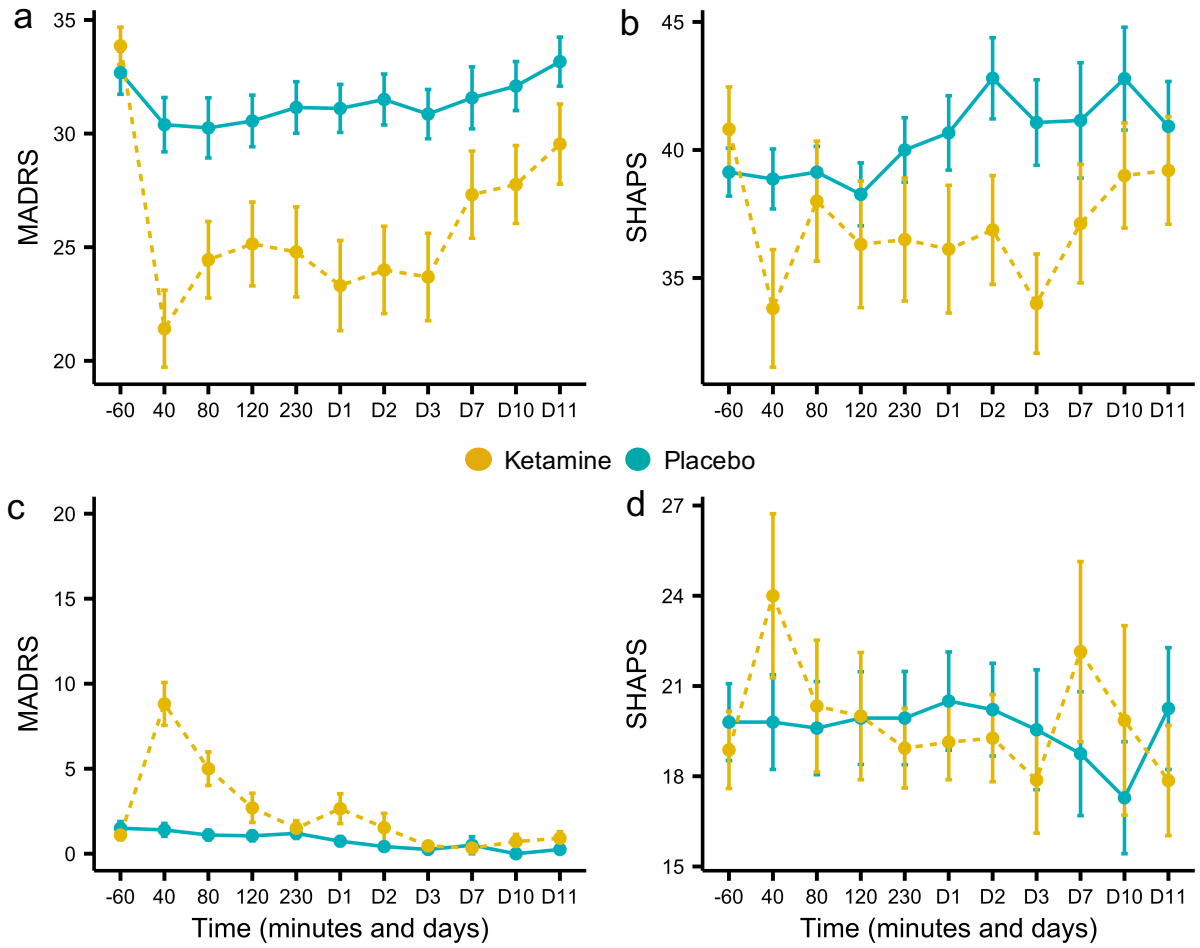

Figure 4.2 Ketamine's effects on symptoms within the current study sample. Participants represent a subsample drawn from a larger study (Nugent et al., 2019). Plots of ketamine's effects on raw Montgomery-Asberg Depression Rating Scale (MADRS) and raw Snaith-Hamilton Pleasure Scale (SHAPS) scores in individuals with treatment-resistant depression (TRD; a and b), and healthy controls (HCs; c and d) are presented.

4.4.2 Ketamine effects on fronto-striatal connectivity

Significant group-by-treatment interactions were observed across all striatal seeds (Table 4.2). Specifically, functional connectivity between VS-left dlPFC, DC-right vlPFC, DCP-pgACC, and VRP-OFC was increased in TRD participants but decreased in HCs post-ketamine (Figure 4.3).

Effect	*Seed*	*Label*	*Size (voxels)*	*Peak x*	*Peak y*	*Peak z*	*F-statistic*	*p-value*
Group * treatment	VS	Right putamen	79	21	5.2	-3.8	$F_{(1,36)}$=27.06	<0.01
		Left dlPFC	51	-28	43.8	31.2	$F_{(1,36)}$=20.54	<0.04
	DC	Right vlPFC	52	52.5	36.8	3.2	$F_{(1,32)}$=20.37	<0.03
	DCP	pgACC	58	7	33.2	-0.2	$F_{(1,36)}$=17.18	<0.03
	VRP	Left OFC	81	-21	26.2	-10.8	$F_{(1,32)}$=28.22	<0.01
		Right OFC	66	28	26.2	3.2	$F_{(1,32)}$=16.96	<0.02

Table 4.2 Striatum-to-whole-brain functional connectivity results. Abbreviations: VS: ventral striatum; DC: dorsal caudate; DCP: dorsal caudal putamen; VRP: ventral rostral putamen; dlPFC: dorsolateral prefrontal cortex; vlPFC: ventrolateral prefrontal cortex; pgACC: perigenual anterior cingulate cortex; OFC: orbitofrontal cortex. All clusters were corrected for multiple comparisons with a cluster-forming threshold of p<0.005 (uncorrected) and family-wise error (FWE) cluster correction at p<0.05 using Monte-Carlo simulation in AFNI.

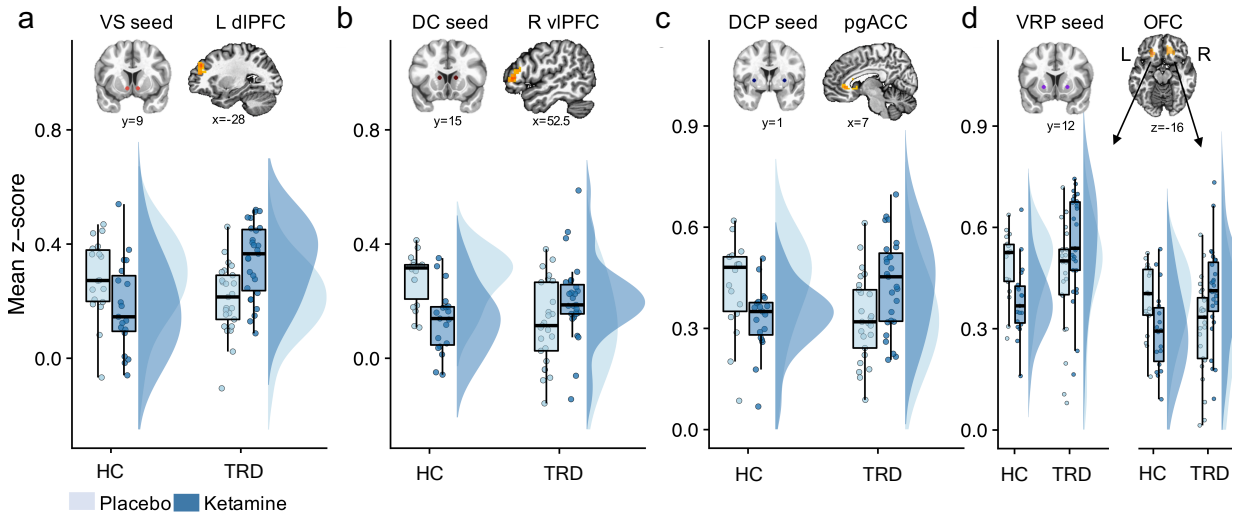

Figure 4.3 Group differences in the effects of ketamine on functional connectivity across four striatal seeds. Ketamine differentially altered functional connectivity between the groups, as reflected in VS-left dlPFC (a), DC-right vlPFC (b), DCP-pgACC (c), and VRP-left/right OFC (d) coupling. This was identified using group-by-treatment F-tests at an FWE cluster-corrected threshold level of p<0.05. Boxplots with individual data points and distributions show that functional connectivity was increased in individuals with treatment-resistant depression (TRD) but reduced in healthy controls (HCs) post-ketamine relative to placebo (a-d). Resting-state functional magnetic resonance imagining scans (rsfMRI) were acquired two days after each infusion. Abbreviations: VS: ventral striatum; DC: dorsal caudate; DCP: dorsal caudal putamen; VRP: ventral rostral putamen; dlPFC: dorsolateral prefrontal cortex; vlPFC: ventrolateral prefrontal cortex; pgACC: perigenual anterior cingulate cortex; OFC: orbitofrontal cortex; L: left; R: right; FWE: family-wise error.

All striatal seed-to-whole-brain functional connectivity analyses were repeated, controlling for age, sex, race, and BMI. Continuous covariates (age and BMI) were mean-centred within each group-by-treatment factor. Results are presented in Table 4.3. To explore what might be driving

the discrepancy between DCP and VRP-right OFC results from the original results, separate DCP and VRP linear mixed models were conducted for each covariate. Results were largely unchanged from the main results (DCP and VRP seeds in Table 4.2) with separate sex, age, and BMI covariate models. However, in both the DCP and VRP models that included only the race covariate, the results mirrored the fully-adjusted effects (Table 4.3), indicating that race was likely driving these deviations from the original results in Table 4.2. Because race was the only covariate that was unbalanced between groups (Table 4.1), future studies should examine whether these effects remain when race is balanced between the groups. However, the original VRP-right OFC cluster (Table 4.1) overlapped with the covariate-controlled VRP-right OFC cluster (Table 4.3), and although the VRP and DCP analyses including covariates differed slightly from the original results, it is important to note that each included covariate reduced the available degrees of freedom. Thus, the covariate-controlled results have lower power to assess ketamine's effects on fronto-striatal circuitry. In summary, these analyses suggest that the fronto-striatal functional connectivity results remained largely unchanged when controlling for covariates, although DCP connectivity may have been influenced by race.

Effect	Seed	Label	Size (voxels)	Peak x	Peak y	Peak z	*F*-statistic	*p*-value
Group * treatment	VS	Right putamen	63	21	5.2	-3.8	$F_{(1,30)}$=27.19	<0.02
		Left dlPFC	54	-28	47.2	17.2	$F_{(1,30)}$=23.40	<0.03
	DC	Right vlPFC	43	52.5	36.8	3.2	$F_{(1,28)}$=22.51	<0.07*
	VRP	Left OFC	85	-21	26.2	-10.8	$F_{(1,28)}$=28.57	<0.01
		Right striatum/ OFC	133	14	19.2	-10.8	$F_{(1,28)}$=28.09	<0.01

Table 4.3 Striatum-to-whole-brain functional connectivity results controlling for sex, age, race and BMI. All clusters were corrected for multiple comparisons with a cluster-forming threshold of $p<0.005$ (uncorrected) and family-wise error (FWE) cluster correction at $p<0.05$ using Monte-Carlo simulation in AFNI resulting in minimum 46 voxels. Abbreviations: VS: ventral striatum; DC: dorsal caudate; VRP: ventral rostral putamen; dlPFC: dorsolateral prefrontal cortex; vlPFC: ventrolateral prefrontal cortex; OFC: orbitofrontal cortex.

*This effect narrowly misses the minimum cluster-corrected voxel size of 46 voxels when all covariates are included but emerges at 47 voxels ($p<0.05$ FWE cluster-corrected) with sex excluded from the model. Sex did not exert a significant main effect or treatment interaction in the DC seed model, but its inclusion decreases degrees of freedom.

All other significant results from each striatal whole-brain functional connectivity analysis and ketamine's group-specific effects are presented in Table 4.4, showing a similar pattern of ketamine primarily affecting fronto-striatal functional connectivity in patients and HCs.

Significant results from each striatal whole-brain functional connectivity analysis								
Effect	**Seed**	**Label**	**Size (voxels)**	**Peak x**	**Peak y**	**Peak z**	***F*-statistic**	***p*-value**
Treatment (Ket > Pla)	VS	Precuneus	71	-0.0	-71.8	+48.8	$F_{(1,49)}$=17.00	<0.01
Group* Infusion order	DC	Insular cortex	62	+42.0	-1.8	-21.2	$F_{(1,32)}$=21.71	<0.02
	DC	Frontal pole	123	+7.0	+61.2	-21.2	$F_{(1,32)}$=19.30	<0.01
Treatment* Infusion order	DC	Precuneus	120	+3.5	-54.2	+17.2	$F_{(1,32)}$=20.88	<0.01
	VRP	Frontal pole	154	-0.0	+61.2	-3.8	$F_{(1,32)}$=26.88	<0.001
Significant post-hoc group-specific ketamine effects from each striatal whole-brain functional connectivity analysis								
Treatment-resistant depressed (TRD) individuals								
Effect	**Seed**	**Label**	**Size (voxels)**	**Peak x**	**Peak y**	**Peak z**	**z-score**	***p*-value**
Ketamine> Placebo	VS	Precuneus	168	-7	-78.8	52.2	3.62	<0.001
		Left OP10/dlPFC	118	-21	57.8	6.8	3.78	<0.01
		Right OP10/ dlPFC	104	24.5	43.8	24.2	4.64	<0.01
		PCC	96	-3.5	-26.2	31.2	4.27	<0.01
	DC	Left OP10/dlPFC	67	-35	40.2	10.2	3.47	<0.02
	VRP	dlPFC	63	-31.5	33.2	31.2	3.43	<0.02
		Right OFC	47	10.5	29.8	-14.2	3.80	<0.05
Healthy controls (HC)								
Placebo> Ketamine	DC	Right vlPFC	52	56	33.2	13.8	-4.76	<0.04
	VRP	Right SFG	70	14	-8.8	62.8	-3.94	<0.01

Table 4.4 Significant results from each striatal whole-brain functional connectivity analysis and post-hoc group-specific ketamine effects. All clusters were corrected for multiple comparisons with a cluster-forming threshold of $p<0.005$ (uncorrected), with a family-wise error (FWE) correction at $p<0.05$ using Monte-Carlo simulation in AFNI. VS: ventral striatum; DC: dorsal caudate; VRP: ventral rostral putamen; dlPFC: dorsolateral prefrontal cortex; PCC: posterior cingulate cortex; vlPFC: ventrolateral prefrontal cortex; OFC: orbitofrontal cortex; SFG: superior frontal gyrus; Ket: ketamine; Pla: placebo. There were no significant clusters from the dorsal caudal putamen seed in TRD or HC individuals, and no significant clusters from the VS seed in HCs at this threshold. Only ketamine>placebo contrast clusters were present for TRD patients and placebo>ketamine contrast clusters in HCs.

4.4.3 Control analyses: ketamine effects on striatal-V1 functional connectivity

Control analyses indicated that ketamine exerted no significant effects on functional connectivity between any of the striatal seeds and the V1 control region (group-by-treatment interaction striatal-V1 functional connections: all Fs<1.99, all ps>0.17; Figure 4.4).

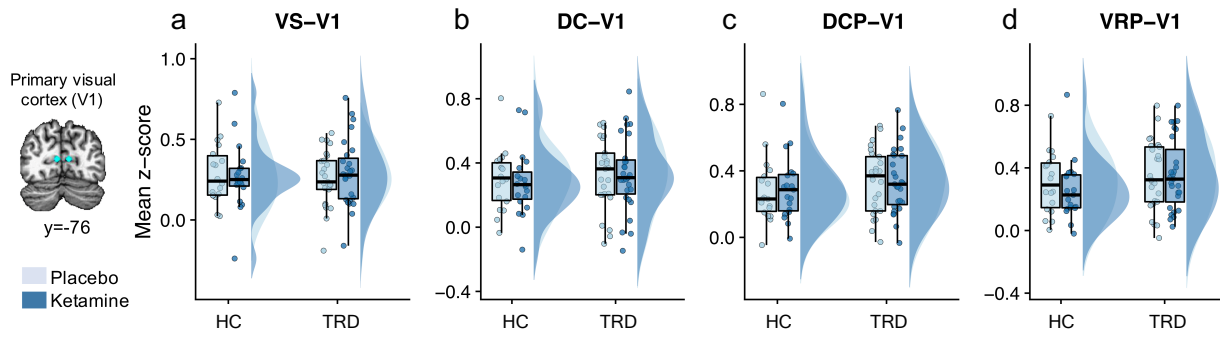

Figure 4.4 Ketamine effects on striatal-V1 functional connectivity. Ketamine had no significant effect on functional connectivity between the striatum and primary visual cortex (V1). Individual data points, box plots, and data distributions are plotted for ventral striatum (VS)-V1 (a), dorsal caudate (DC)-V1 (b), dorsal caudal putamen (DCP)-V1 (c), and ventral rostral putamen (VRP)-V1 (d) functional connectivity post-ketamine and post-placebo for healthy controls (HCs) and individuals with treatment-resistant depression (TRD).

4.4.4 Inflammatory markers (CRP)

There were no significant correlations between peripheral inflammation and BMI within the TRD (all r<0.37, all p>0.07) or HC groups (all r<0.41, all p>0.08). BMI was therefore not included as a covariate in any subsequent analyses. No significant main effects on CRP levels were noted for group ($F_{(1,48.50)}$=1.11, p=0.30), treatment ($F_{(1,45.52)}$=0.37, p=0.55), or group-by-treatment interaction ($F_{(1,\ 45.52)}$=1.61, p=0.21; Figure 4.5a). No significant differences in CRP levels between groups were found at baseline either ($t_{(49)}$=0.72, p=0.48; Figure 4.5b).

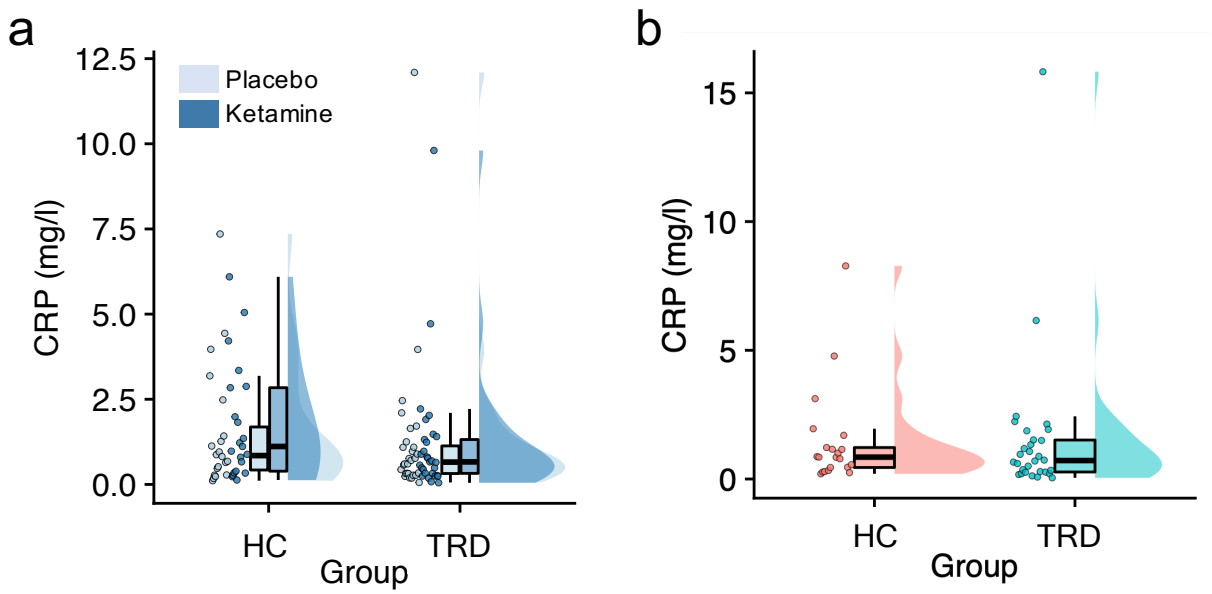

Figure 4.5 C-Reactive Protein (CRP) effects. There were no significant effects of ketamine on CRP levels (a) or differences between groups at baseline (-60 minutes before the first infusion; b). Raw CRP levels are presented but analyses were conducted on log-transformed data. HC: Healthy control; TRD: Treatment-resistant depression.

A negative association was observed between ΔCRP and VRP-right OFC ΔFC in HCs (r=-0.64, *p*=0.007; Figure 4.6), such that increased CRP levels post-ketamine correlated with decreased VRP-right OFC functional connectivity. However, this was not the case for TRD participants (r=-0.07, *p*=0.77; Figure 4.6). The difference in correlation coefficients between HCs and TRD participants narrowly missed significance, although it should be noted that statistical power for this comparison is low (Fisher's Z test: z=1.91, *p*=0.06). No other relationships between ΔCRP and ΔFC post-ketamine were significant (all absolute r<0.45, all *p*>0.08). No significant relationship was observed between averaged baseline CRP levels and change in SHAPS scores post-ketamine in patients (r=-0.14, *p*=0.61, N=15), or between averaged baseline CRP levels and ketamine-induced changes in fronto-striatal circuitry in patients (all absolute r<0.35, all *p*>0.11, N=22).

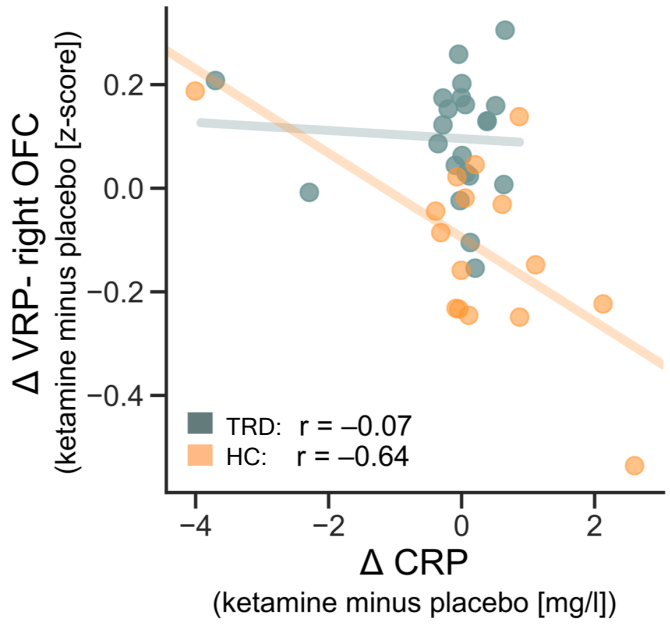

Figure 4.6 The relationship between ketamine-induced changes in peripheral inflammation with changes in VRP-OFC functional connectivity. Data are plotted separately for healthy controls (HCs; p=0.007) and individuals with treatment-resistant depression (TRD; p=0.77). CRP: C-Reactive Protein; VRP: Ventral Rostral Putamen; OFC: Orbitofrontal cortex; Δ: ketamine minus placebo.

4.4.5 Association with symptoms on Day 2

No significant correlations were noted between ΔMADRS and ΔFC at Day 2 in TRD participants (all absolute r<0.20, *p*>0.38). However, a significant correlation was observed between post-ketamine improvement (i.e., reduction) in SHAPS score and post-ketamine increases in DC-right vlPFC functional connectivity on Day 2 (Figure 4.7a; r=-0.60, *p*=0.04; other ΔSHAPS and striatal-PFC ΔFC associations at Day 2: all absolute r<0.16, *p*>0.62).

4.4.6 Association with symptoms on Day 10

No significant correlations were observed between ΔMADRS and ΔFC at Day 10 in TRD participants (all absolute r<0.32, *p*>0.18). Improvement in Day 10 SHAPS scores were associated with post-ketamine increases in DCP-pgACC connectivity (Figure 4.7b; r=-0.64, *p*=0.02). All other correlations between fronto-striatal ΔFC and Day 10 ΔSHAPS showed a similar, but non-

significant pattern (DC-right vlPFC: r=-0.56, *p*=0.06; VRP-right OFC: r=-0.54, *p*=0.07; VS-left dlPFC: r=-0.47, *p*=0.12; VRP-left OFC: r=-0.34, *p*=0.28; Figure 4.7c-f).

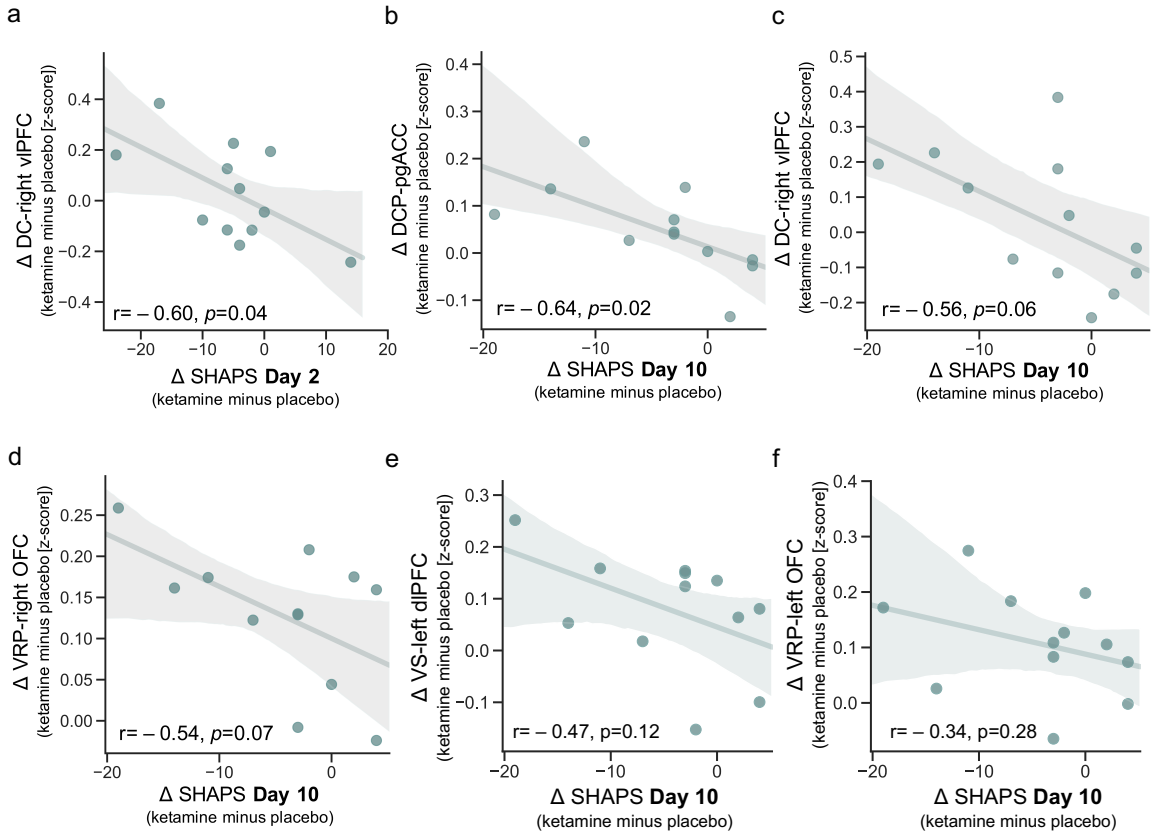

Figure 4.7 Associations between changes in fronto-striatal circuitry and improvements in SHAPS scores. Associations between ketamine-induced changes in DC-right vlPFC connectivity and SHAPS scores two days post-infusion (scan day; a), and 10 days post-infusion (b-f) in individuals with treatment-resistant depression. Negative SHAPS scores indicate post-ketamine improvements compared with post-placebo and positive functional connectivity scores indicate increased functional connectivity post-ketamine compared with post-placebo. Shaded area represents estimated 95% confidence interval. SHAPS: Snaith-Hamilton Pleasure Scale; DC: dorsal caudate; vlPFC: ventrolateral prefrontal cortex; DCP: dorsal caudal putamen; pgACC: perigenual anterior cingulate cortex; VRP: ventral rostral putamen; OFC: orbitofrontal cortex; Δ: ketamine minus placebo.

4.5 Discussion

This study sought to examine how ketamine affects fronto-striatal neural circuitry in TRD participants relative to HCs. Ketamine was found to modulate fronto-striatal circuitry in a diagnosis-specific manner. In TRD participants, ketamine increased functional connectivity between the caudate and prefrontal regions (left dlPFC and right vlPFC) commonly implicated in cognitive processes and between the putamen and prefrontal regions (pgACC and OFC) commonly implicated affective processes. However, in HCs, functional connectivity with the striatum in these same frontal regions decreased post-ketamine. Notably, this was not simply due to a global shift in functional connectivity across the brain, as previously suggested (Driesen et al., 2013), but specific to the PFC (Abdallah et al., 2017); in particular, striatal-visual cortex connectivity was not similarly affected by ketamine. These results underscore the complexities of ketamine's neural effects.

Previous studies found that ketamine improves anhedonia symptoms and increases glucose metabolism in the VS, putamen, and dorsal ACC, extending into the sgACC and dlPFC, in individuals with treatment-resistant MDD and bipolar disorder (Lally et al., 2014; Lally et al., 2015; Nugent et al., 2014). Similarly, ketamine has been shown to increase striatal responses during emotional processing (Murrough et al., 2015) and global brain connectivity in the striatum and PFC (Abdallah et al., 2017). The present study extends these findings by showing that, compared with placebo, ketamine increased functional connectivity specifically within this fronto-striatal network in TRD participants. This is an important extension, given that psychiatric disorders may be better characterized as disruptions in circuit-level networks than in individual regions, as behaviours are thought to be achieved through multiple neural regions acting in concert (Treadway & Pizzagalli, 2014).

While ketamine can improve motivational symptoms in MDD, it often produces mild symptoms of impaired motivation, such as anhedonia and lassitude, in HCs (Ballard et al., 2018; Driesen et al., 2013; Lally et al., 2014; Lally et al., 2015; Nugent et al., 2019; Pollak et al., 2015; Stone et al., 2008; Thiebes et al., 2017). This pattern dovetails with recent findings showing that ketamine

restores dysfunctional neural mechanisms underlying emotional processing in depression but shifts these in the opposite direction in HCs (Reed et al., 2018, 2019). These diagnosis-dependent effects suggest that the initial functioning level of the neural circuit may be key to determining neurobiological response to ketamine. Ketamine also promotes glutamate signalling within cortico-limbic-striatal circuits and potentiates dopaminergic activity within the striatum and PFC (Duman & Aghajanian, 2012; Kokkinou et al., 2018; Yao et al., 2018), suggesting that glutamatergic signalling and downstream modulation of dopaminergic activity within the fronto-striatal circuitry may form a crucial part of ketamine's neural effects (Belujon & Grace, 2014; Murrough et al., 2015).

A secondary goal of the study was to explore whether inflammatory processes, as assessed via CRP levels, affected ketamine-induced shifts in fronto-striatal connectivity (Cooper et al., 2018; Felger & Treadway, 2017; Miller & Raison, 2015). Contrary to our hypotheses, there was no clear evidence that ketamine-induced fronto-striatal connectivity changes depended on peripheral inflammatory processes. Increased CRP levels post-ketamine were associated with reduced VRP-right OFC functional connectivity, but only in HCs. This implies that downregulation of some aspects of the brain's reward system may be associated with changes in inflammatory processes in HCs. This finding is in line with previous studies suggesting that inflammatory processes are particularly associated with OFC functioning (Felger et al., 2016; Yin et al., 2019), although our OFC region was more lateral than found in previous studies. In addition, ketamine did not significantly affect CRP levels, nor did the association between change in VRP-right OFC and change in CRP levels post-ketamine differ significantly from the non-significant association in TRD participants. The identified association should therefore be considered tentative.

To date, ketamine's effects on reward-circuitry have not been extensively examined despite strong theoretical and empirical grounds (Alexander et al., 2019; Ballard et al., 2018; Duman & Aghajanian, 2012; Gould et al., 2019; Lally et al., 2014; Lally et al., 2015). Echoing the present results, a previous study found reduced functional connectivity within cortico-striatal nodes in

healthy non-human primates 24 hours post-ketamine (Lv et al., 2016). In contrast, another study found the opposite pattern in human HCs (Dandash et al., 2015). An important implication of the present study, however, is that investigations of ketamine's antidepressant mechanisms should be interpreted with caution when based on healthy populations only, as previously reported (Nugent et al., 2019; Reed et al., 2018, 2019).

A number of limitations of this study merit comment. Firstly, ketamine-induced increases in fronto-striatal connectivity would be expected to relate to improvements in anhedonia in TRD participants, but a significant relationship was detected only with DC-right vlPFC connectivity. That said, only a subset of the sample had SHAPS measures at both placebo and ketamine sessions, meaning that the study may have been underpowered to detect such associations. Similarly, the manner in which neural changes may relate to symptom changes in HCs was not investigated, given that all post-ketamine symptom changes had subsided to baseline levels by the day of the rsfMRI scan. However, the HC findings are consistent with previous studies demonstrating that decreased global connectivity in the striatum and decreased cerebral blood flow in the PFC are associated with increasing levels of negative symptoms/anhedonia immediately post-ketamine administration in HCs (Driesen et al., 2013; Pollak et al., 2015).

Secondly, few participants had symptom and CRP data at both rsfMRI scans. Likewise, CRP and rsfMRI data were not available at the same timepoint. Due to the exploratory nature of these correlational analyses, the data were not corrected for multiple comparisons. In addition, larger sample sizes than tested here are required to establish robust brain-behaviour associations (Marek et al., 2022). As such, the symptom and CRP associations should be considered preliminary and require further confirmation.

Finally, in contrast to previous cross-sectional studies (Chamberlain et al., 2019; Haapakoski et al., 2015; Miller et al., 2009), the participant population did not differ from HCs in terms of baseline CRP levels, suggesting that the current study captured a subgroup of TRD participants not characterized by dysfunctional inflammatory functioning. This may have obscured our

ability to properly examine relationships with inflammation, as TRD participants did not exhibit a large range of CRP levels. Future studies should seek to recruit a more heterogeneous sample in terms of baseline inflammation levels to determine whether ketamine might exert important effects mediated by inflammatory processes.

In summary, the present study suggests that low fronto-striatal connectivity is normalized in TRD participants but disrupted in HCs post-ketamine, and preliminary evidence suggest that this largely occurs independently from peripheral inflammatory processes. This highlights the importance of including HCs as a normative model to draw comparisons. Considering the crucial role that fronto-striatal circuitry plays in goal-directed behaviours, these findings may be particularly relevant for the rapid and sustained reorientation of motivational states observed post-ketamine.

5 The effect of ketamine on reward and punishment processing in TRD

5.1 Abstract

The aim of this chapter was to address the main question of the thesis, asking which reward and punishment behavioural mechanisms may underlie ketamine's beneficial effects in TRD patients. Based on the literature suggesting impairments in reinforcement learning, decision-making, and willingness to exert effort in depression, four tasks spanning these processes were chosen based on acceptable psychometric properties identified in Chapter 2: a restless four-armed bandit task; a reward/punishment bias task (adapted from the PRT); the clock task, testing exploratory behaviour; and a physical effort task. Case-control comparisons in a sample prior to treatment revealed no significant differences between healthy individuals (total N=13) and MDD patients (total N=21) on any behavioural measures. These tasks were then administered to nine TRD individuals who underwent a randomised, double-blind, placebo-controlled crossover trial of ketamine (0.5mg/kg), tested one day post-infusion. Prior exposure to a sub-anaesthetic dose of ketamine significantly increased exploratory behaviour in the clock task, in line with predictions; notably, this pattern was observed in every individual. Ketamine also increased punishment learning rate in the four-armed bandit task, but did not significantly affect response bias or physical effort processing, although the limited statistical power of the analysis should be noted. Unfortunately, this also precluded examination of relationships between ketamine's effects on anhedonia and reward processing. These very preliminary results suggest that ketamine might exert its beneficial effects through improvements in goal-directed exploratory behaviours. Due to the exploratory nature of this study, future research is needed to replicate and extend these results and better understand how they may relate to the previously observed anti-anhedonic effects of ketamine.

5.2 Introduction

Multiple studies have suggested that a single sub-anaesthetic dose of ketamine may improve symptoms of anhedonia (Lally et al., 2014; Lally et al., 2015). However, symptom scales do not offer the mechanistic insight needed to understand the cognitive components that underlie ketamine's anti-anhedonic effects. This is necessary if we wish to improve existing treatments or target existing ones better. Prominent theories emphasise the importance of alterations of components of reward and punishment processing in MDD, as discussed in Chapter 1. Therefore, the current chapter focuses on several candidate mechanisms, involving RL, motivation to exert effort and decision-making, that may underlie ketamine's anti-anhedonic effects.

Despite theoretical and empirical accounts implicating the importance of reward-related processing in anhedonia (Admon & Pizzagalli, 2015; Bekhbat et al., 2022; Bishop & Gagne, 2018; Borsini et al., 2020; Cooper et al., 2018; Der-Avakian & Markou, 2012; Der-Avakian & Pizzagalli, 2018; Eshel & Roiser, 2010; Felger & Treadway, 2017; Husain & Roiser, 2018; Huys et al., 2021; Kieslich et al., 2022; Lucido et al., 2021; Pizzagalli, 2014; Rizvi et al., 2016; Rømer Thomsen et al., 2015; Treadway, 2016; Treadway et al., 2019; Treadway & Pizzagalli, 2014; Treadway & Zald, 2011, 2013; Wang et al., 2021; Zald & Treadway, 2017; Zhang et al., 2016), few studies have examined how ketamine affects behavioural reward and punishment processes. Preliminary data in a small sample of TRD patients and rodents have suggested that ketamine does not improve effort-related decision-making (Griesius et al., 2020; Lally, 2015). However, these studies used a task where reward and effort were not orthogonal and additionally included a probabilistic element (Treadway et al., 2009), complicating interpretation of performance. In the same TRD patient study, ketamine also did not significantly modulate learning in a static RL task using high and low probabilities of reward (Lally, 2015). However, it is unclear if ketamine might affect learning in more uncertain environments, which likely more closely mimic real-life, or computational measures of RL, which allow dissecting the precise cognitive components driving behaviour (Huys et al., 2016). A recent study in healthy marmoset monkeys indicated that ketamine can acutely (post 2 hours) increase reward responsiveness on

the PRT (Wooldridge et al., 2020). On this task depressed patients commonly lack a bias toward the more rewarded stimuli, as compared with healthy individuals, which has been associated with anhedonia (Huys et al., 2013). This raises the prospect that ketamine might have beneficial effects on this aspect of reward processing in depression.

Besides the above study in TRD patients, no studies have specifically examined whether ketamine affects cognitive and computational markers of reward and punishment processing in TRD patients in the context of randomised, double-blind, placebo-controlled experiments. Several suitable tasks were identified to address this, and examined for acceptable psychometric properties in Chapter 2, to maximise sensitivity of measurement in the context of a crossover (within-subjects) design. From Chapter 2, the current study included the restless four-armed bandit task (Daw et al., 2006), measuring reward/punishment learning and sensitivity; a physical effort-based decision-making task (Bonnelle et al., 2016), to probe willingness to exert effort; a reward/punishment bias task, measuring response bias to rewards and punishments, adapted from the PRT (Pizzagalli et al., 2005); and the clock task (Frank et al., 2009), assessing exploratory behaviours. It was reasoned that these tasks cover aspects of reward and punishment which may be particularly important in anhedonia (see Chapter 1), and thus represent central candidate mechanisms of ketamine's anti-anhedonic effects. Importantly, these tasks were identified as having at least one measure of interest with acceptable test-retest properties, as assessed in Chapter 2, and were thus deemed suitable for repeated testing.

These four tasks allowed us to test the hypothesis that ketamine's beneficial effects are driven by changes in reward and punishment processing. Based on previous studies indicating lower reward responsiveness (PRT), lower reward sensitivity and learning (bandit task), lower willingness to exert effort (physical effort task), and lower goal-directed exploratory behaviours (clock task) in anhedonia and MDD (Halahakoon et al., 2020; Husain & Roiser, 2018; Huys et al., 2021; Huys et al., 2013; Strauss et al., 2011), several predictions were made. Specifically, it was hypothesised that: 1) at baseline and compared with healthy individuals, patients would show

lower reward response bias, as tested in the reward/punishment bias task, lower reward learning and sensitivity in the bandit task, lower willingness to exert physical effort and lower exploratory behaviours in the clock task; and that 2) these effects would correlate with anhedonic symptom severity in patients. It was further predicted that 3) a single sub-anaesthetic dose of ketamine would remediate impairments in TRD in the above processes.

5.3 Methods

5.3.1 Participants

Thirteen HCs and twenty-three MDD patients were recruited from various study protocols at the NIH, Bethesda, Maryland, USA. All participants were initially enrolled under a screening protocol during which the SCID (First et al., 2002a, 2002b) was used to evaluate and diagnose participants. If eligible, participants were allocated to various active study protocols at the NIMH ETPB. Most participants included in the current chapter were drawn from a larger clinical trial of ketamine ('Neuropharmacologic Imaging and Biomarker Assessments of Response to Acute and Repeated-Dosed Ketamine Infusions in Major Depressive Disorder'; NCT03065335). All participants completed behavioural measures at baseline, and two of the HCs and thirteen of the TRD patients were admitted to an inpatient psychiatric unit at the NIMH and enrolled in the ketamine clinical trial.

Inclusion criteria for MDD patients in the ketamine clinical trial included a current DSM-5 diagnosis of MDD; a baseline score of at least 20 on the MADRS (Montgomery & Åsberg, 1979) and less than 12 on the Young Mania Rating Scale (YMRS) (Young et al., 1978) at the initial screening and before any ketamine infusions. Patients were also required to have had at least one current or previous lack of response to an adequate antidepressant trial (electroconvulsive therapy included). Before testing, all patients were free of psychotropic medication for at least 2 weeks (5 weeks for fluoxetine, 3 weeks for aripiprazole). Patient exclusion criteria included a current diagnosis of bipolar disorder or any psychotic disorder. Exclusion criteria for HCs included a current or past history of any DSM-5 axis I disorder. All participants were deemed to be in good physical health with no poorly-controlled medical problems, as determined by medical history, physical examination, blood labs, chest x-ray, electrocardiogram, toxicology, and urinalysis. No participants met criteria for drug or alcohol use disorder, dependency or abuse (caffeine/nicotine was allowed) within the preceding three months (patients) or lifetime (HCs). For all participants additional inclusion criteria included: 18-65 years of age; no pregnancy or nursing in women; use of effective birth control in women during study participation; and weight less than 119kg. One patient was excluded due to not meeting the

minimum score on the MADRS before testing. Additionally, three patients withdrew before completing the post-infusion assessments but completed the baseline assessment, leaving nine patients in the final analysis.

Additional participants for the baseline measures were tested under other study protocols. Ten HCs were enrolled in a ketamine sub-study assessing ketamine metabolites, and one HC was enrolled in a test-retest study, part of a 'development' protocol used for various studies. Inclusion and exclusion criteria of HCs for these protocols were identical to the ones listed above. Three additional patients were tested under the developmental protocol with identical inclusion/exclusion criteria for patients as listed above, except that they did not need to meet the failed antidepressant trial criteria. Finally, seven patients were tested under a screening protocol. Current psychotropic medication in patients was not an exclusion criterion in the screening protocol. One of these seven patients was excluded in the current study due to active alcohol abuse. Out of the remaining six, four were on antidepressant medication. See Table 5.1 and Table 5.2 for a detailed breakdown of participant study allocation and characteristics. All participants provided written informed consent, and the study was approved by the NIH Combined Central Nervous System IRB.

5.3.2 Case-control baseline study design

A baseline behavioural assessment was completed to assess case-control comparisons on various reward and punishment processing tasks (see below). Patients who did not enrol in the ketamine clinical trial study were tested only once to provide baseline datapoints. Table 5.1 describes the final allocation of participants across task measures and study protocols.

Case-control baseline study								
	Study protocol							
	Healthy controls (HC)				Patients (MDD)			
Tasks	Ketamine clinical trial	Ketamine metabolite	Test-retest	HC Total N	Ketamine clinical trial	Development	Screening	MDD Total N
Bandit	2	10	1	13	12	3	6	21
Physical effort	2	10	0	12	11	0	6	17
Clock	2	10	1	13	12	0	6	18
Rew/pun bias	2	9	1	12	12	3	6	21

Table 5.1 Final participant allocation across study protocols for baseline measures. Baseline measures were used from the ketamine clinical trial. The ketamine metabolite study involved healthy controls only, in which they completed a baseline assessment followed by an open-label ketamine infusion (0.5mg/kg) one day later and lumbar puncture to examine ketamine metabolites from cerebrospinal fluid. Only data from the baseline assessment is analysed from the ketamine metabolite study due to the low number of participants completing post-infusion measures (N=8) and the lack of an assessment on practice effects on measures tested on consecutive days. In the test-retest study, participants completed the task battery on two consecutive days, with only the baseline assessment included here. In the development study, unmedicated patients were tested on baseline tasks once. In the screening protocol, medicated (N=4) and unmedicated patients who did not proceed to the ketamine clinical trial due to exclusion criteria completed the baseline assessment. The bandit task is short for the four-armed bandit task. MDD: Major Depressive Disorder; N: Number of participants; Rew: Reward; Pun: Punishment.

5.3.3 Ketamine study design

The ketamine study employed a double-blind, placebo-controlled, crossover design with three phases (Figure 5.1). Infusions were administered through intravenous tubing in the forearms over 40 minutes using identical injections to ensure blinding. Participants' baseline session occurred in phase 1, approximately one week before their first infusion. In phase 2, participants were randomised to receive either a single intravenous infusion of a subanaesthetic-dose of ketamine hydrochloride (0.5 mg/kg) or placebo (0.9% saline solution) during the first session (day 0) and the alternative treatment in the second session (day 7) conducted one week later. Participants additionally received an identical ketamine and placebo infusion three and four weeks after their first infusion (not depicted in Figure 5.1). Thus, in total, participants received four drug infusions (two ketamine and two placebo) in phase 2. The current study procedures of assessing the effect of ketamine, compared with placebo, on various reward and punishment tasks, were completed only following the first two infusions. These testing sessions occurred one day post-infusion, as ketamine produces the greatest anti-anhedonic effect at this timepoint (Lally et al., 2014). Following phase 2, patients, but not HCs, were enrolled in phase 3, which consisted of biweekly infusions of either ketamine (0.5 mg/kg) or an active control (0.1

mg/kg ketamine) for four weeks to assess the safety and efficacy of repeated ketamine administrations. Patients completed the current study measures at the end of phase 3 as well. However, only phase 2 post-infusion behavioural data were analysed due to the low number of participants completing phase 3 (total N=8) and difficulty in unblinding patients' treatment allocation in phase 3. Similarly, no data from HCs in phase 2 were analysed due to the small number of HCs with post-infusion data (N=2). Data were analysed from the first two infusions in phase 2 on patients who completed both placebo and ketamine infusions (N=9).

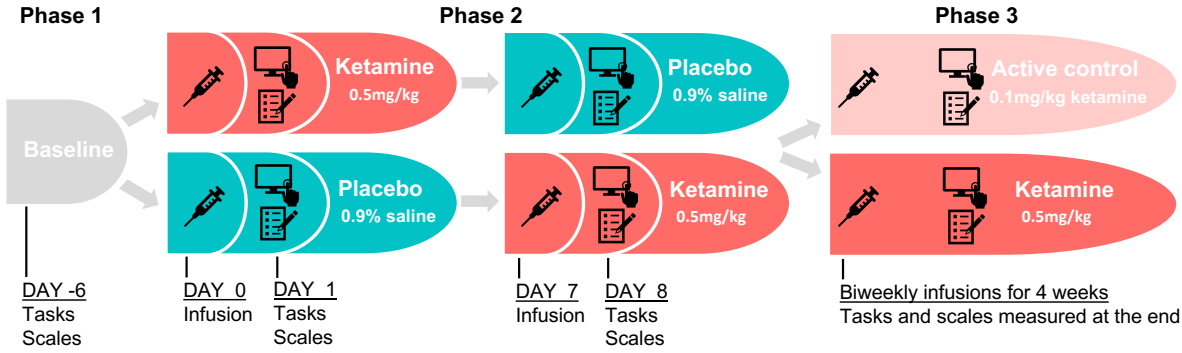

Figure 5.1 Ketamine study design. Approximately one week prior to the first infusion, participants completed a battery of reward and punishment tasks along with psychometric scales in phase 1. In phase 2, participants were randomised to receive either ketamine or placebo on their first infusion and the alternative treatment one week later. Task and scale measures were again administered one day post their first and second infusion in phase 2. Following their second infusion, participants received two more infusions (ketamine and placebo) one week apart (infusion three on day 14 and infusion four on day 21). Participants were not tested following infusion three and four on the behavioural measures presented here and these infusions are therefore omitted in the figure.

5.3.4 Unblinding

At the time of writing, the ketamine study was an active trial, and thus formal unblinding of drug randomisation was not possible. In lieu of this, preliminary unblinding of phase 2 was conducted based on blood pressure values monitored by a study researcher not involved in the analysis of the current data, as ketamine is known to temporarily, but robustly, increase blood pressure (Riva-Posse et al., 2018). To supplement these drug session guesses, symptom scores from the Clinician-Administered Dissociative States Scale (CADSS) (Bremner et al., 1998) were analysed 40-minutes post-infusion, as ketamine has shown to temporarily increase CADSS scores 40 minutes post-infusion (Ballard & Zarate, 2020). The CADSS is a 23-item clinician-

administered measure of perceptual, behavioural, and attentional alterations occurring during dissociative experiences.

5.3.5 Symptom scales

The following symptom scales were administered at baseline and post-infusion: MADRS (Montgomery & Åsberg, 1979), the Beck Depression Inventory Second Edition (BDI-II) (Beck et al., 1996), the SHAPS, the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006), the Dysfunctional Attitudes Scale Short Form 2 (DAS-SF2) (Beevers et al., 2007), the Fatigue Severity Scale (FSS) (Kleinman et al., 2000), the General Self-Efficacy Scale (GSE) (Schwarzer & Jerusalem, 1995), the Life Orientation Test- Revised (LOT-R) (Scheier et al., 1994), the State-Trait Anxiety Inventory (STAI) (Spielberger, 1989), and the Apathy Motivation Index (AMI) (Ang et al., 2017). When scales were administered post-infusion, participants were asked to indicate how they felt since the last time the rating was administered.

The MADRS, SHAPS and TEPS scales were the primary scales of interest at the post-infusion assessments. The MADRS is a 10-item clinician-rated instrument for the evaluation of general depressive symptoms and was analysed 60 minutes before each infusion, 120, 230 minutes and one, two, three, and six days post-infusion, with higher scores indicating more severe depression. The SHAPS is a 14-item self-report scale assessing hedonic capacity with higher scores indicating greater levels of anhedonia. Data for the SHAPS was available at baseline, 120, 230 minutes and one, two, three, and six days post-infusion. Similarly, the TEPS is a self-report measure of anhedonia, which attempts to dissociate its anticipatory and consummatory aspects, with lower scores indicating more severe levels of anhedonia. The scale consists of 18 items in total (10 items for anticipatory anhedonia, eight for consummatory anhedonia) and was analysed at baseline, 120, 230 minutes and one, two, three, and six days post-infusion.

The scales of secondary interest were the BDI-II, DAS-SF2, FSS, GSE, LOT-R, STAI, and AMI, where higher scores indicate greater severity of the construct the scale assesses, except in GSE and LOT-R, where lower scores indicate greater severity. Data for these scales were available at

baseline and one-day post-infusion. The BDI-II is 21-item self-report scale measuring various aspects of depressive symptoms, the DAS-SF2 is a 9-item self-report scale of various dysfunctional attitudes such as negative and perfectionist attitudes, the FSS is a 9-item self-report measure of fatigue severity, the GSE is a 10-item self-report psychometric scale of self-efficacy, the LOT-R is a 10-item self-report questionnaire to assess generalized optimism versus pessimism, STAI is a self-report measure of both state (20 items) and trait (20 items) anxiety, and the AMI is an 18-item self-report measure of motivational deficits in behavioural, social and emotional areas designed for use in the general population.

5.3.6 Reward and punishment tasks

Participants were administered a battery of tasks assessing various components of reward and punishment processing. All tasks were presented in a randomised order at baseline and post-infusion sessions. The gambling task, which showed excellent reliability in Chapter 2, was not included in this battery due to time constraints. Priority was given to tasks that, based on the literature, were hypothesised to be most relevant for assessing cognitive processes underlying anhedonia; in this regard, fewer prior studies indicate disruption of loss/risk aversion processes in anhedonia compared with the other tasks.

All tasks were presented on a laptop using MATLAB (R2015b, The MathWorks, Inc., Natick, MA, United States) with either Psychtoolbox (http://psychtoolbox.org) or Cogent (Wellcome Centre for Human Neuroimaging and Institute of Cognitive Neuroscience, UCL, London, U.K.). Participants were reimbursed $40 and could win a bonus of up to $40 based on performance for each session. At the end of each session the computer randomly picked 100 trials across all the tasks to calculate the performance-based bonus. The bonus was revealed to the participant at the end of the final session.

5.3.6.1 Four-armed bandit task

The restless four-armed bandit task assesses the independent effects of rewards and punishments on decisions (Daw et al., 2006; Seymour et al., 2012). On each trial participants

were asked to choose one out of four bandits (represented as boxes), which would display one out of four possible outcomes following a choice: reward (green token), punishment (red token), neither reward nor punishment (empty box) or both reward and punishment (red and green token; Figure 5.2). The probability of reward and punishment outcomes varied over time (with a slow random walk) independently of one another within each bandit, and independently between bandits (meaning that it is possible for both reward and punishment to be delivered simultaneously). Participants were instructed on the non-stationary and independent nature of choice outcomes and were told that the goal was to maximize gains and minimize losses. The task lasted around 15 minutes with 200 trials in total. This was the identical version of the task described in Chapter 2.

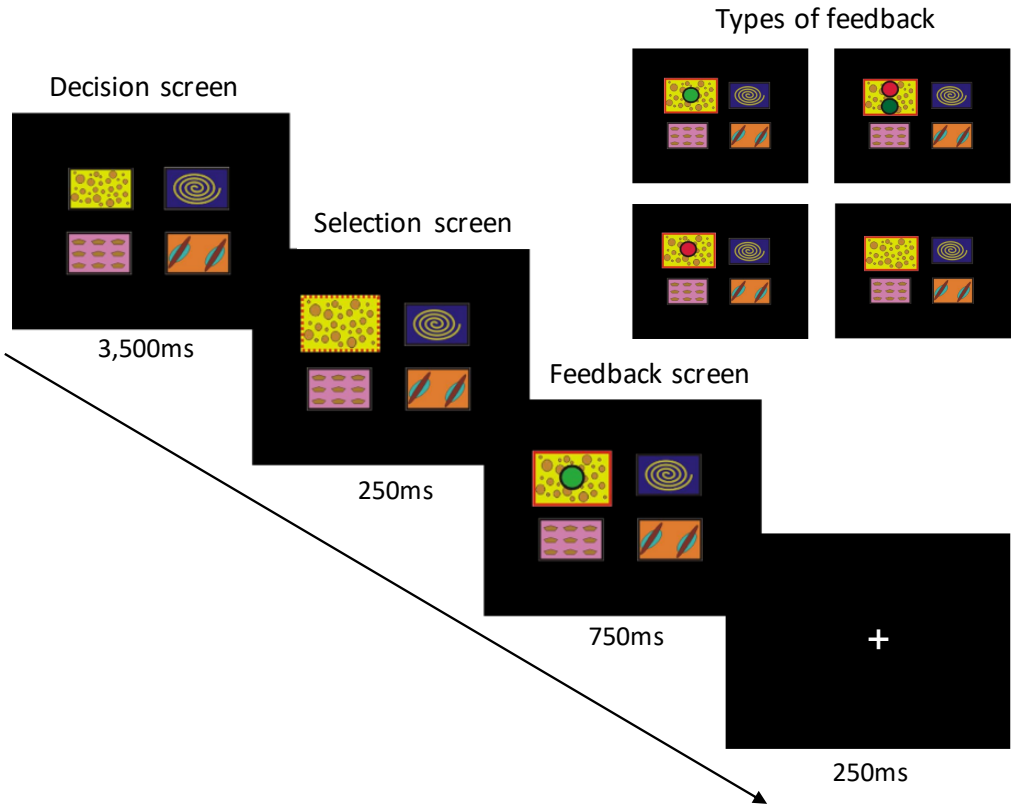

Figure 5.2 Example trial of the restless four-armed bandit task. On each trial, participants chose one out of four bandits and received one out of four possible outcomes: reward (green token), punishment (red token), neither reward nor punishment (empty box) or both reward and punishment (red and green token).

5.3.6.2 Physical effort task

The physical effort task measures motivation to exert physical effort for rewards (Bonnelle et al., 2016; Bonnelle et al., 2015). A different version of the task was used from Chapter 2. Here participants were required to squeeze a hand dynamometer with their non-dominant hand in order to obtain rewards (instead of button pressing in Chapter 2), with the amount of reward available and effort required varying parametrically. Participants were presented with challenges comprising different combinations of reward and effort, and could choose whether to engage in the challenge or not. Before the task commenced, participants completed a practice session in which they squeezed at their maximum strength on six trials to estimate their maximum voluntary contraction (MVC). This ensured that the effort levels were calibrated to each participant's force capacity. The purpose of the calibration phase was not explicitly conveyed to participants, instead being framed as a practice phase.

In the main part of the task, participants were presented with an offer indicating how much physical effort (20, 40, 60 or 80% of their MVC) they had to exert for a set amount of reward (3, 6, 9 or 12 points; Figure 5.3). The offer was shown in the form of an apple tree where the number of apples in the tree indicated the reward available in the trial, and the effort level was shown with a yellow line on the tree trunk such that one had to squeeze above the line and hold continuously for at least three seconds to collect the apples (points). Thus, a higher effort level was depicted with the yellow line placed at a higher level on the tree trunk, signifying that greater force would be needed to obtain the reward. Participants were free to accept/reject offers based on their perception of the effort-reward combination. If a trial was rejected, the task moved on to the next trial. A failed or rejected trial resulted in zero points. To avoid possible fatigue effects, 25% of accepted trials skipped the effort execution phase. No points were won on the skipped trials, and participants were informed that some accepted trials would randomly be skipped.

The task lasted for approximately 20 minutes and contained 5 trials per effort x reward combination, with each combination randomly presented throughout the task, resulting in a

total of 80 trials. Participants were instructed that the goal was to win as many points as possible and that they could take breaks between each block (five blocks with 16 trials).

The design of the physical effort task administered in the test-retest study in Chapter 2 was based on this task (but instead using keypresses for physical effort, and with one fewer level of each of the reward and effort factors). The tasks were therefore very similar, with the assumption that the reliability would be similar.

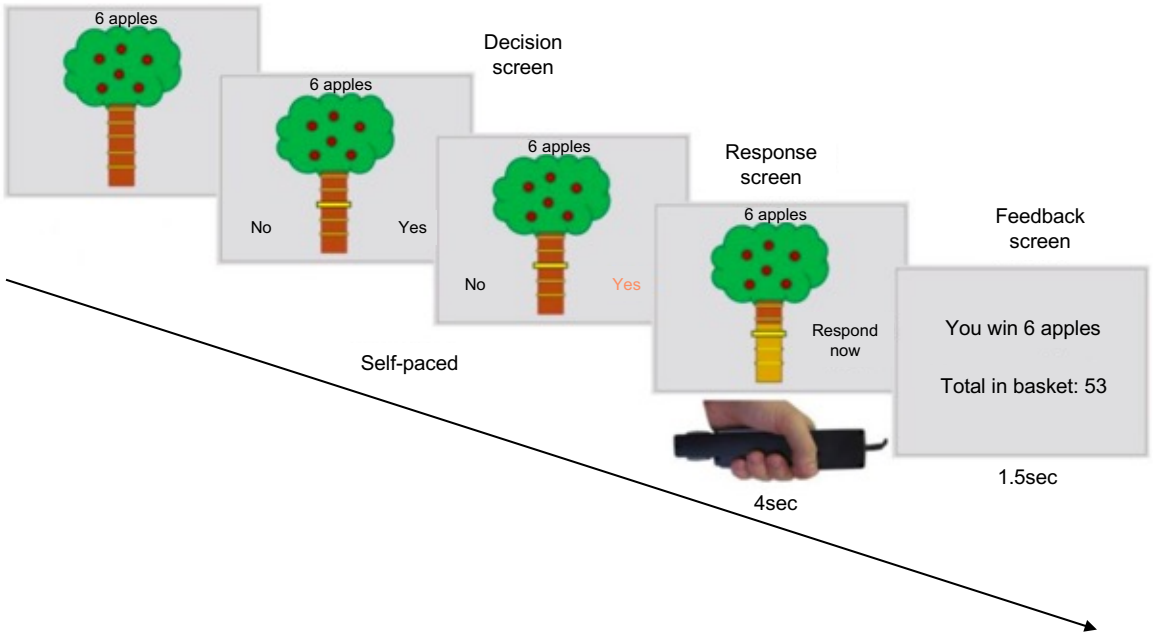

Figure 5.3 Example trial of the physical effort task. On each trial participants were presented with a tree on which a yellow line on the trunk represented the required effort level, and the number of apples represented the number of available points. Participants decided if they wanted to accept or reject the offer based on the number of points and effort level. If the offer was declined, no points were won, and the task moved on to the next trial. If an offer was accepted, participants were required to squeeze a hand dynamometer above the yellow line for 3 consecutive seconds to win the points.

5.3.6.3 Clock task

The clock task measures uncertainty-driven exploration and go/no-go learning (Frank et al., 2009; Moustafa et al., 2008). On each trial, a clock was presented with a rotating arm and participants were asked to stop it within a five second period by pressing the spacebar (Figure

5.4). Depending on when they chose to stop it, participants could win different numbers of points. The task consisted of four conditions with different EV by manipulating reward probability and magnitude of each condition: 1) IEV, promoting slower response times to maximise reward; 2) DEV, promoting faster response times to maximise reward; 3) CEV, reward probability decreased over time while reward magnitude increased over time (baseline condition controlling for individual differences in motor responding); and 4) CEVR, the opposite of the CEV condition.

There were four blocks in total, each corresponding to one of the task conditions. At the beginning of each block participants were told that they would interact with a new clock (also indicated by a different colour clock face which was randomised across subjects), for which they had to learn the optimal style of responding (e.g., fast or slow) to maximize rewards. The condition blocks were presented in a random order across participants. There were 160 trials in total (40 trials/ condition) with each trial lasting five seconds regardless of when a response was executed, and the task lasted approximately 15 minutes. This was the identical version of the task described in Chapter 2.

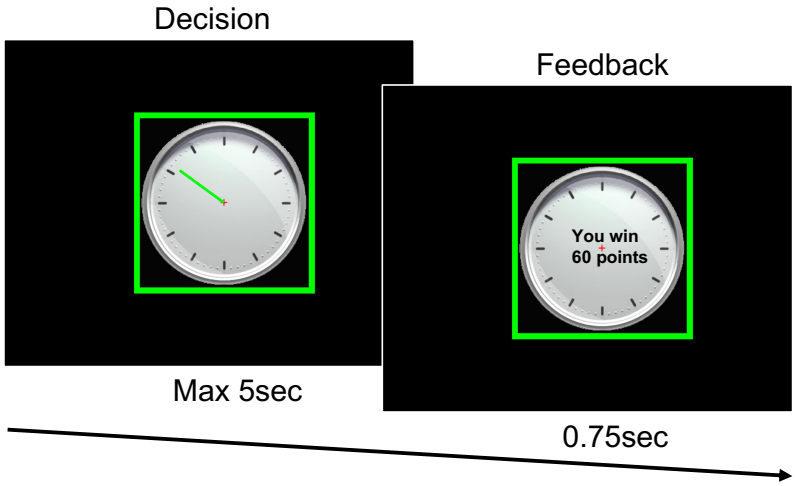

Figure 5.4 Example trial of the clock task. On each trial, participants were presented with a clock face on which the clock arm would rotate for five seconds and participants had to learn the optimal style of responding (e.g., stop the arm early or late) to maximize rewards. The task consisted of four conditions with different expected values to promote different types of responding.

5.3.6.4 Reward/punishment bias task

The reward/punishment bias task is a modified version of the PRT (Pizzagalli et al., 2005), which is based on signal detection theory. This version measures reward and punishment response bias using a difficult visual discrimination paradigm. During the task, participants were asked to indicate whether a presented bar was short (11.5mm) or long (13mm; Figure 5.5). Asymmetric reward and punishment reinforcement schedules were used to induce response biases for the more frequently rewarded/punished stimulus. The small perceptual difference between a short and a long bar creates stimulus ambiguity, which promotes responses toward selecting the more frequently rewarded stimulus (as on average this will lead to greater rewards) and the more frequently punished stimulus (as responding correctly to this stimulus will lead to fewer losses).

On each trial, a short or a long bar was presented for 100ms, and the bar could be either horizontal or vertical. The task consisted of two valence conditions (reward and punishment), where, for example, correct responses on the horizontal bars could be rewarded and incorrect responses on the vertical bars could lead to losses (valence condition assignment to horizontal/vertical bars were counterbalanced across participants). Participants were informed that correct responses to one stimulus (short or long bar) in the reward condition would be three times more likely to result in a reward (+5 points) than correct responses to the other stimulus (short or long bar). Similarly, in the punishment condition, participants were instructed that one stimulus (short or long bar) would be three times more likely to result in a loss (-5 points) for an incorrect response compared with incorrect responses to the other stimulus (short or long bar). Unlike the original specification of the task, participants were instructed which stimulus was the 'best' (i.e., the one reinforced more frequently), with the aim of removing the learning component of the original task. The assignment of the frequent versus rare stimulus to short/long bars was counterbalanced across valence conditions and within the valence condition. They were further instructed that a correct response in the reward condition would not always lead to a reward and an incorrect response in the punishment condition would not always lead to a loss. Participants were asked to respond using the left/right arrow

keys on horizontal trials and the up/down arrow keys on vertical trials, with key assignments to short/long bars counterbalanced across participants.

The task consisted of 3 blocks with 100 trials per block (50 reward and 50 punishment trials totalling 150 trials per valence condition) with reward and punishment trials presented in an interleaved random order across blocks. Participants were free to take breaks between blocks, and the task lasted about 20 minutes.

The reward/punishment bias task was thus modified from the original PRT in the following important aspects: 1) a punishment condition was added to assess how response bias is modulated by losses versus rewards, 2) a bar in a box was used instead of a mouth in a face as depressed individuals might assign affective valence to faces, and 3) the learning requirement was removed such that individuals were explicitly instructed on which stimulus was more frequently reinforced in order to reduce task difficulty and dissociate any bias effects from learning ability. This was the identical version of the task described in Chapter 2. Although it was not possible to examine reliability of this task in Chapter 2 due to a coding error, previous studies indicate that response bias on the PRT is reliable over long testing intervals (20-120 days range; r=0.57) (Pizzagalli et al., 2005).

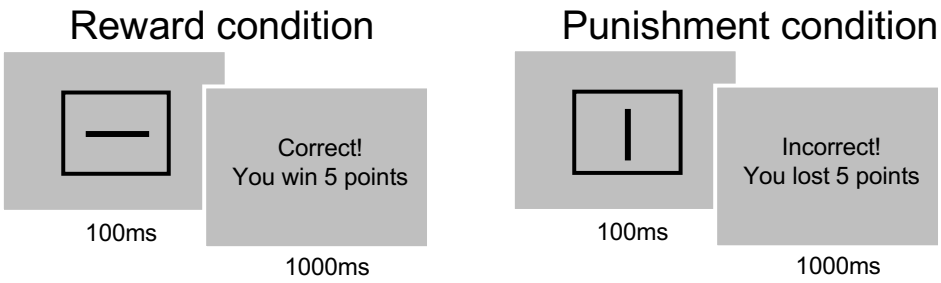

Figure 5.5 Example trials of the reward/punishment bias task. On each trial, participants were flashed with a bar and had to correctly identify if it was short or long. The task consisted of both reward and punishment conditions (either horizontal or vertical bars) where either the long or short bar was more frequently rewarded for correct responses or punished for incorrect responses. Reward and punishment conditions were presented in an interleaved order.

5.3.7 Data analysis

5.3.7.1 Symptom scales

Pearson correlation coefficients were used to explore correlations between scales at baseline within healthy controls and patients separately. These analyses were mainly conducted to better characterise the patient sample. To examine the effect of ketamine versus placebo on scales with multiple timepoints (MADRS, SHAPS, TEPS), a linear mixed effects model with fixed effects of time, treatment, and their interaction was used with a compound covariance structure. No random effect was estimated here since the model would not converge. For the MADRS scale, the baseline scores (60 minutes prior to each infusion) were included as a covariate (fixed main effect) to correct for baseline symptom levels. The main time-point of interest was day one (24h post-infusion) since ketamine's antidepressant and anti-anhedonic effects have previously shown to be greatest at this timepoint (Kryst et al., 2020; Lally et al., 2014) and the task battery was administered on this day as well. Uncorrected simple effects tests within the linear model were therefore performed to examine ketamine effects on symptoms at day one. To examine ketamine versus placebo effects on scales with only one timepoint (one day post-infusion: BDI-II, DAS-SF2, FSS, GSE, LOT-R, STAI, AMI), paired t-tests were conducted. Cohen's d_z effect sizes are presented for the day one effects. For all scales, these effect sizes were based on a paired t-test. Thus, for the MADRS, SHAPS and TEPS scales, these only provide approximate effect sizes.

Pearson correlation coefficients were used to examine relationships between a set of scales defined *a priori* (SHAPS, TEPS, AMI and BDI) and task performance at baseline in patients. These scales were prioritised to reduce the number of multiple tests performed and because they were deemed to be of primary interest as scales measuring general depression and various aspects of anhedonia. The BDI was chosen over the MADRS since BDI data were available for all patients as compared with the MADRS. Correlations were only performed within the patient cohort as 1) the patient and HC group were almost perfectly non-overlapping on most symptom scales (with the HCs generally scoring at the extreme lower end; Figure 5.7), and 2) there were insufficient participants to explore correlations within the HC group. No correlations between

task measures and scales were conducted in the post-infusion sessions due to the sample size being too low to conduct meaningful analyses (N=9).

5.3.7.2 Restless four-armed bandit task

As in Chapter 2, model-agnostic analyses focussed on examining the probability of repeating a choice after win-only, loss-only and no outcomes (number of repeated choices/total choices in that category). For the bandit case-control comparison, a mixed ANOVA was conducted with a between-subjects factor group (HC, patients) and a within-subjects factor outcome (win, loss, neither). Model-agnostic derived measures of reward sensitivity (probability to stay after reward minus probability to stay after neither) and punishment sensitivity (probability to stay after punishment minus probability to stay after neither) were used to correlate with symptom scales. To assess the effect of ketamine on task performance, a repeated-measures ANOVA was conducted with the within-subjects factors being outcome (win, loss, neither) and treatment (ketamine, placebo).

For the computational model analysis, we initially fit the previously identified winning RL model from Chapter 2, the *Bandit4arm_lapse* model from the hBayesDM package. This model included five parameters: a reward learning, punishment learning, reward sensitivity, punishment sensitivity, and lapse parameter. However, this model showed high trade-off (i.e., correlations) between the lapse and other parameters in the current dataset, indicating non-identifiability of these parameters. In addition, in Chapter 2 it was demonstrated that the lapse parameter showed poor reliability and recoverability, thus the second-best winning model from Chapter 2 was used here. This model (called *Bandit4arm_4par* in the hBayesDM package) had similar reliabilities as the reported model in Chapter 2 (*Bandit4arm_4par* reliability: reward learning ICC=0.62, 95% CI 0.41-0.76; punishment learning rate ICC=0.65, 95% CI 0.45-0.78; reward sensitivity ICC=0.55, 95% ICC 0.33-0.72; punishment sensitivity ICC=0.44, 95% ICC 0.19-0.64) and comprised the same parameters as the *Bandit4arm_lapse* but excluded the lapse parameter (Aylward et al., 2019):

$$Value_{t(i)}^{rew} = Value_{t(i)}^{rew} + Reward\ Learning\ Rate \times Prediction\ Error_{t(i)}^{rew} \quad (1)$$

$$Value_{t(i)}^{pun} = Value_{t(i)}^{pun} + Punishment\ Learning\ Rate \times Prediction\ Error_{t(i)}^{pun} \quad (2)$$

'rew' and 'pun' refers to the reward (1,0) and punishment (0,-1) values on each trial (t) for a given bandit (i).

$$if\ i = chosen\text{: } Prediction\ Error_{t(i)}^{rew} = Reward\ Sensitivity \times Reward\ Outcome(t) - Value_{t-1(i)}^{rew} \quad (3)$$

$$if\ i = unchosen\text{: } Prediction\ Error_{t(i)}^{rew} = -Value_{t-1(i)}^{rew}$$

$$if\ i = chosen\text{: } Prediction\ Error_{t(i)}^{pun} = Punishment\ Sensitivity \times Punishment\ Outcome(t) - Value_{t-1(i)}^{pun} \quad (4)$$

$$if\ i = unchosen\text{: } Prediction\ Error_{t(i)}^{pun} = -Value_{t-1(i)}^{pun}$$

The subjective reward and punishment values were passed through a softmax function to estimate the probability of choosing a given bandit on each trial (j represents all bandits):

$$Choice\ Probability = \frac{\exp\left(Value_{t(i)}^{rew} + Value_{t(i)}^{pun}\right)}{\sum_j \exp\left(Value_{t(i)}^{rew} + Value_{t(i)}^{pun}\right)}$$

The case-control baseline data were fit with the *Bandit4arm_4par* model using a single hierarchical prior (i.e., both patients and healthy controls were fit together), as this approach is more conservative than estimating the groups separately. The same model was used to fit the post-infusion data with a single prior again (placebo and ketamine data together). Independent t-tests were used to assess any group differences on mean parameter point estimates at baseline. The individual mean posterior parameter estimates of patients were used to correlate with symptom scales at baseline. Paired t-tests were used to assess the differential effects of ketamine and placebo on parameters.

5.3.7.3 Clock task

As in Chapter 2, model-agnostic measures of go and no-go learning were computed from the mean response times of the IEV, DEV, and CEV conditions (go learning=DEV minus CEV; no-go learning=IEV minus CEV) (Moustafa et al., 2008). For the case-control analysis, a mixed-effects ANOVA was performed with a between-subjects factor of group (HC, MDD) and within-subjects factor condition (go learning, no-go learning). Trial-to-trial variance was measured as an index of overall RT swings (i.e., change in response times) and a model-agnostic proxy for uncertainty-driven exploration (manifested behaviourally as RT swings):

$$\sqrt{\sum(RT(i) - RT(i+1))^2/(n-1)},$$

where i is the trial number and n is the total number of trials. An independent t-test was used to compare groups on overall RT swings. A repeated-measures ANOVA with treatment (ketamine, placebo) and learning condition (go and no-go learning) as within-subjects factor was used to assess the effect of ketamine on learning. A paired t-test was used to examine the effect of ketamine, compared with placebo, on overall RT swings.

5.3.7.4 Physical effort task

As in Chapter 2, the main model-agnostic measure of interest in the physical effort task was the probability to accept an offer. For the case-control comparison analysis, a mixed effects ANOVA was used with a between-subject factor group (HCs, patients) and within-subject factors reward (3, 6, 9, 12 points) and effort (20, 40, 60, 80%). Due to the low sample size in the post-infusion sessions, the equivalent within-subjects ANOVA analysis was not possible. Linear contrasts of effort and reward were computed to assess the degree to which reward and effort influenced behaviour:

$$Reward\ sensitivty = \frac{1.5 \times p(accept\ at\ 12) + 0.5 \times p(accept\ at\ 9) - 0.5 \times p(accept\ a\ 6) - 1.5 \times p(accept\ at\ 3)}{overall\ p(accept)}$$

$$Effort\ sensitivty = \frac{1.5 \times p(accept\ at\ 80\%) + 0.5 \times p(accept\ at\ 60\%) - 0.5 \times p(accept\ a\ 40\%) - 1.5 \times p(accept\ at\ 20\%)}{overall\ p(accept)}$$

An independent t-test was used to assess group differences and a paired t-test was used to assess ketamine versus placebo effects on these linear contrasts. A paired t-test was additionally performed to examine the effect of ketamine, compared with placebo, on the overall probability to accept an offer.

5.3.7.5 Reward/punishment bias task

As in previous studies, model-agnostic measures were derived from signal detection theory (Pizzagalli et al., 2008; Pizzagalli et al., 2005). Response bias is the main variable of interest in this task and describes the preference of one stimulus over the other due to the reinforcement schedule. Response bias was calculated separately for each valence condition where a high response bias in the reward condition corresponds to a preference for the more frequently rewarded stimulus and a high punishment response bias corresponds to a preference for the more frequently punished stimulus (as being correct on this stimulus allows avoiding greater losses). Response bias was calculated as follows:

$$Response\ bias = 0.5 * log\left(\frac{Frequent_{correct} * Rare_{incorrect}}{Frequent_{incorrect} * Rare_{correct}}\right),$$

where 'frequent correct' corresponds to correct responses on the stimulus that was more frequently reinforced (rewarded or punished) and 'rare correct' corresponds to correct responses on the stimulus that was less frequently reinforced. In previous studies with the original version of this task, 'frequent' corresponds to the 'rich' stimulus and 'rare' corresponds to the 'lean' stimulus.

To dissociate differences in response bias from potential differences in the perceptual ability to distinguish between the short and long stimulus, task discriminability was assessed (proxy of task difficulty) and is computed as:

$$Task\ discriminability = 0.5 * log(\frac{Frequent_{correct} * Rare_{correct}}{Frequent_{incorrect} * Rare_{incorrect}})$$

Higher task discriminability arises as the task is perceived to be easier. Due to some values being 0 (and the log of 0 being undefined), 0.5 was added to each cell in both response bias and task discriminability calculations. Trials were excluded if participants responded to vertical trials using horizontal arrow keys and vice versa (mean number of trials excluded: HC=3.61% trials, MDD=2.23%, ketamine=0.62%, placebo=1.81%).

For the case-control baseline analysis, mixed-effects ANOVAs with between-subjects factor group (HC, MDD) and within-subjects factor valence (reward, punishment) were conducted on response bias and task discriminability. One patient was excluded in the baseline session (resulting in N=20 patients) due to only making "left" responses on horizontal trials and "up" responses on vertical trials, indicating that they did not engage with the task.

Repeated-measures ANOVAs with treatment (ketamine, placebo) and valence (reward, punishment) were conducted to examine ketamine effects on response bias and task discriminability. One patient had a faulty recording during their placebo session and the same patient who had to be excluded in the baseline session was excluded in their post-infusion sessions for the same identified reason. These exclusions resulted in N=7 patients for the post-infusion analysis. However, including or excluding the patient who did not engage in the task did not substantially change the results.

5.3.7.6 General data analysis

Data were processed in Matlab (R2019b) and analysed in SPSS (v28, IBM Corp, Armonk, NY) and R (v.4.1.2). Computational modelling of the four-armed bandit task was completed with the hBayesDM package (https://github.com/CCS-Lab/hBayesDM) (Ahn et al., 2017) for R (v.4.1.2) in RStudio (v.2021.01.1), using hierarchical Bayesian modelling in Stan (v.2.21.1). Cohen's *d* effect size is presented for case-control comparisons and Cohen's d_z for within-group comparisons (Lakens, 2013). If any demographic variable was significantly different between HCs and patients, it was mean-centred and initially added as a covariate in all the case-control analyses.

However, no covariate had a significant main effect on task behaviour and therefore they were dropped from all analyses to retain degrees of freedom; analyses including covariates are therefore not reported. When the equal variances assumption was violated for independent t-tests, the Welch test was used. Greenhouse-Geisser corrected values of degrees of freedom are reported throughout for repeated-measures ANOVAs if sphericity assumptions were violated. Infusion order was not included as a factor in any post-ketamine analyses due to the low sample size. For all analyses, $p<0.05$ (two-tailed) was considered statistically significant, and due to the exploratory nature of the study no correction for multiple comparisons was applied.

5.3.7.7 Power analysis

We initially anticipated that 50 patients would be recruited for the clinical trial, as stated on ClinicalTrials.gov (NCT03065335). However, for various reasons, most notably Covid-19, less than one-fifth of the originally planned sample size had been collected at the time of writing. Conducting a retrospective sensitivity power analysis, with a sample size of N=9 patients, this study had 80% power to detect a ketamine effect size of 1.07 (two-tailed paired t-test, alpha level=0.05), calculated in G*Power (Faul et al., 2007).

5.4 Results

5.4.1 Symptom scales and demographics: Case-control baseline comparison

Participant characteristics at baseline are presented in Table 5.2. The only demographic variable that was significantly different between groups was age, with patients being on average almost 11 years older than healthy controls.

	Healthy controls (N=13)		**MDD Patients (N=21)**			
	Mean	**SD**	**Mean**	**SD**	***t*-value**	***p*-value**
Age	28.77	6.82	39.62	13.40	3.12	0.004
Years of education	17.79 (N=12)	2.82	17.00 (N=17)	3.81	0.62	0.55
Age of onset	NA	NA	15.95	7.41		
Length of illness (years)	NA	NA	23.76	12.70		
Failed antidepressant treatments	NA	NA	8 (N=17)	4.5		
	N	**%**	**N**	**%**		
Female	7	54	9	43	0.39	0.53
TRD	NA	NA	18 (N=19)	95		
Currently medicated	NA	NA	4	19		

Table 5.2 Demographic and clinical variables for the baseline case-control analysis. MDD: Major Depressive Disorder; N: Number; SD: Standard Deviation; TRD: Treatment-resistant depression.

Figure 5.6 depicts the correlations between symptom scales in healthy controls and patients separately. Of interest here, TEPS-A and TEPS-C correlated only moderately in patients (r=0.54, p=0.01), indicating that these two scales may be measuring somewhat different aspects of anhedonia in the current patient population. SHAPS was also more strongly related to TEPS-C (r=-0.72, p<0.001) than TEPS-A (r=-0.58, p=0.005), although this difference was not statistically different (Dunn and Clark's z =0.90, p=0.37) (Silver et al., 2004). MADRS and SHAPS correlated moderately in patients (r=0.54, p=0.02), as did MADRS and TEPS-C (r=-0.56, p=0.01), while MADRS and TEPS-A were only weakly and non-significantly correlated (r=-0.23, p=0.34). This indicates that anticipatory anhedonia, as measured by the TEPS-A, might be assessing relatively specific aspects of motivational symptoms not captured by MADRS, SHAPS or TEPS-C in this group of patients. Similarly, AMI-BA, which measures the propensity to self-initiate goal-directed behaviours (i.e., apathy), showed relatively weak-to-moderate correlations with MADRS (r=0.41, p=0.09), SHAPS (r=0.31, p=0.20), TEPS-A (r=-0.14, p=0.56) and TEPS-C (r=-0.18,

p=0.45), suggesting that this scale captures unique features of motivational impairments not related to general depressive symptoms or anhedonia in this patient cohort. All the subscales of the AMI showed relatively weak correlations with each other, with the strongest between AMI-SM and AMI-BA (r=0.53, *p*=0.02). In HCs, the strongest observed scale associations were between TEPS-A and TEPS-C (r=0.87, *p*<0.001), between BDI-II and STAI-State (r=0.83, *p*<0.001), AMI-SM and TEPS-A (r=0.81, *p*<0.001), and AMI-SM and TEPS-C (r=0.80, *p*<0.001).

Figure 5.7 shows the difference between patients and HCs on all the scales. The only scale that showed an almost complete overlap in scores between groups was the AMI-ES (measuring feelings of positive and negative affection), where only a small difference was detected between groups (Cohen's *d*=0.25), which did not achieve significance. Interestingly, compared with the other anhedonia scales, patients seemed to have less pronounced consummatory anhedonia (TEPS-C), consistent with reports from behavioural studies (Kieslich et al., 2022). The symptom scales on which patients showed the most pronounced difference on from HCs, besides MADRS (part of the inclusion criteria), were BDI-II, STAI-Trait (these two also correlated strongly in patients; Figure 5.6) and AMI-BA.

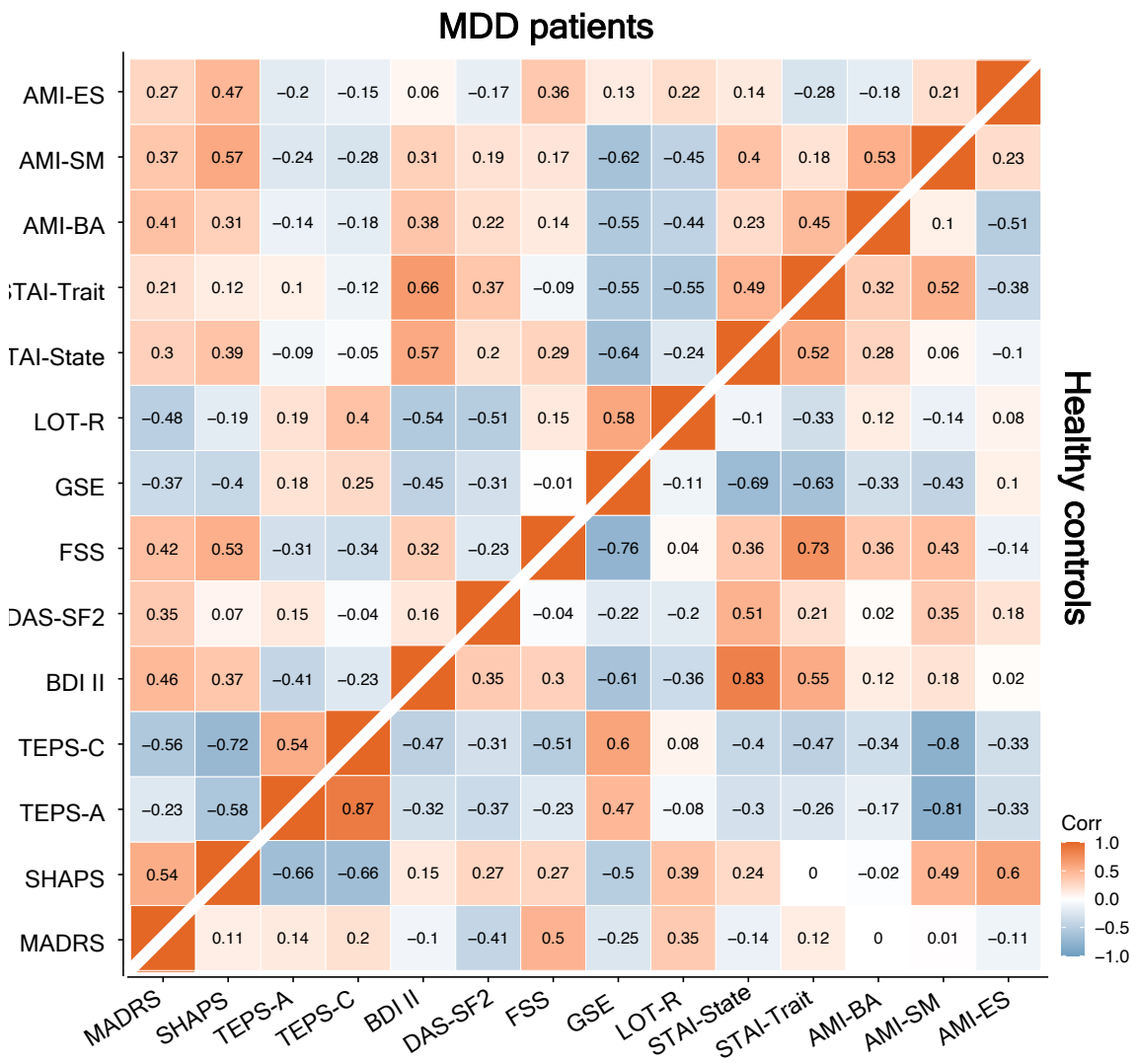

Figure 5.6 Correlations between symptom scales at baseline separately for healthy controls (bottom) and patients with major depressive disorder (MDD; top). Higher scores indicate greater severity on the symptom dimension measured by all scales, except the TEPS, GSE and LOT-R, where lower scores indicate greater severity. Data is presented for 13 healthy controls and 21 patients, with fewer datapoints available for the MADRS (HC N=11, MDD N=19), DAS-SF2 (MDD N=20), LOT-R (MDD N=20), STAI (MDD N=19), and AMI (MDD N=19). Abbreviations: MADRS: Montgomery-Åsberg Depression Rating Scale; SHAPS: Snaith-Hamilton Pleasure Scale; TEPS-A: Temporal Experience of Pleasure Scale Anticipatory Subscale; TEPS-C: Temporal Experience of Pleasure Scale Consummatory Subscale; BDI-II: Beck Depression Inventory Second Edition; DAS-SF2: Dysfunctional Attitude Scale Short Form 2; FSS: Fatigue Severity Scale; GSE: General Self-Efficacy Scale; LOT-R: Life Orientation Test-Revised; STAI-State: State-Trait Anxiety Inventory-State Subscale; STAI-Trait: State-Trait Anxiety Inventory-Trait Subscale; AMI-BA: Apathy Motivation Index Behavioural Activation; AMI-SM: Apathy Motivation Index Social Motivation; AMI-ES: Apathy Motivation Index Emotional Sensitivity.

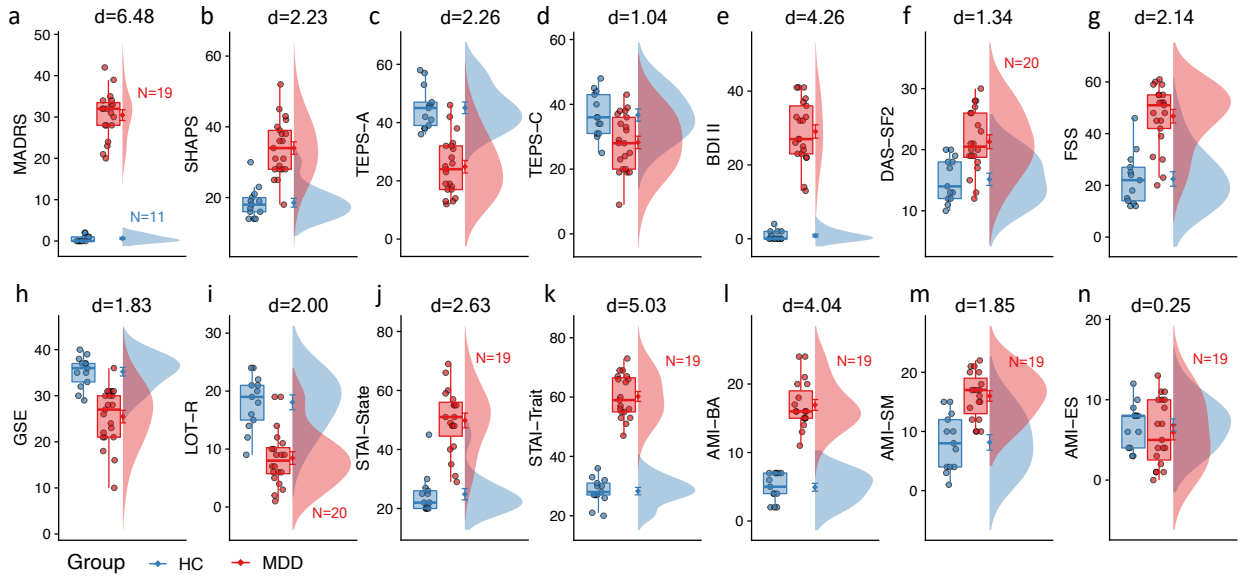

Figure 5.7 Case-control comparison on symptom scales at baseline. Individual data points, boxplots, data distributions and mean±standard error of the mean are plotted for thirteen healthy controls (HC) and 21 patients with major depressive disorder (MDD) except when the sample size (N) is specified differently in the figure. Cohen's *d* effect sizes are presented for the difference between HCs and MDD. Higher scores indicate greater severity on the symptom dimension measured by all scales, except the TEPS, GSE and LOT-R, where lower scores indicate greater severity. Abbreviations: MADRS: Montgomery-Åsberg Depression Rating Scale (a); SHAPS: Snaith-Hamilton Pleasure Scale (b); TEPS-A: Temporal Experience of Pleasure Scale Anticipatory Subscale (c); TEPS-C: Temporal Experience of Pleasure Scale Consummatory Subscale (d); BDI-II: Beck Depression Inventory Second Edition (e); DAS-SF2: Dysfunctional Attitude Scale Short Form 2 (f); FSS: Fatigue Severity Scale (g); GSE: General Self-Efficacy Scale (h); LOT-R: Life Orientation Test-Revised (i); STAI-State: State-Trait Anxiety Inventory-State Subscale (j); STAI-Trait: State-Trait Anxiety Inventory-Trait Subscale (k); AMI-BA: Apathy Motivation Index Behavioural Activation (l); AMI-SM: Apathy Motivation Index Social Motivation (m); AMI-ES: Apathy Motivation Index Emotional Sensitivity (n).

5.4.2 Four-armed bandit task: Case-control baseline comparison

5.4.2.1 Model-agnostic measures

There was an expected significant main effect of outcome on subsequent choice ($F_{(2,64)}$=46.14, p<0.001, partial η_p^2=0.59), such that the probability of staying was different after each outcome type (loss<neither<win; all p<0.001). Overall probability of staying was numerically higher in patients than healthy controls, although this narrowly missed significance (main effect of group: $F_{(1,632)}$=3.76, p=0.06, partial η_p^2=0.11), as did the group-by-outcome interaction ($F_{(2,64)}$=2.50, p=0.09, partial η_p^2=0.07; Figure 5.8). There were no significant correlations between any of the symptom scales and probability of staying following wins (all absolute r<0.23, p>0.42) or losses (all r<0.40, p>0.09) in patients.

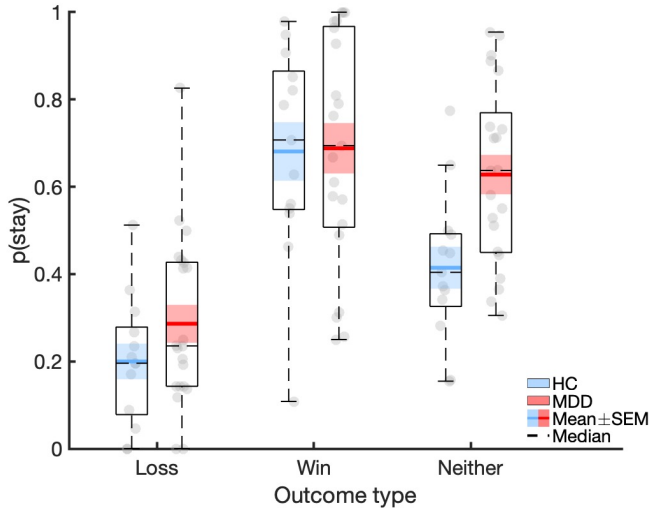

Figure 5.8 Performance on the four-armed bandit task at baseline (model-agnostic measures). Boxplots showing the probability of staying after different outcomes in healthy controls (HC; N=13) and patients with major depressive disorder (MDD; N=21). SEM: Standard error of the mean.

5.4.2.2 Computational model

There were no significant group differences between any of the parameters in the RL model of the four-armed bandit task (reward learning: $t(32)=0.21$, $p=0.84$, $d=0.07$; punishment learning: $t(32)=1.27$, $p=0.21$, $d=0.45$; reward sensitivity: $t(27.84)=1.35$, $p=0.19$, $d=0.40$; punishment sensitivity: $t(32)=0.56$, $p=0.58$, $d=0.20$; Figure 5.9).

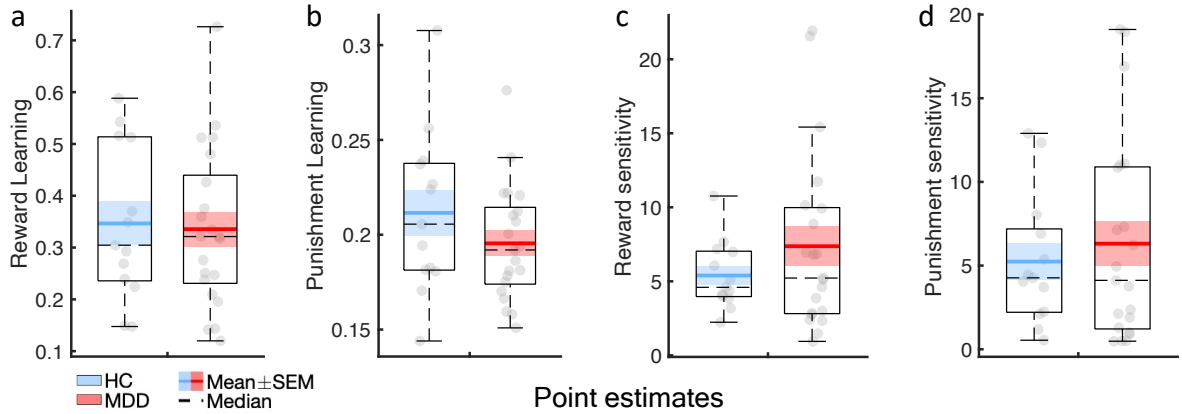

Figure 5.9 Case-control comparison at baseline on the four-armed bandit reinforcement learning model. Mean posterior point estimates of subject-specific reward learning (a), punishment learning (b), reward sensitivity (c) and punishment sensitivity (d) parameters are presented for healthy controls (HC; N=13) and patients with major depressive disorder (MDD; N=21). SEM: Standard error of the mean.

Contrary to predictions, higher reward learning rates were associated with *greater* SHAPS scores in patients (r=0.64, *p*=0.002), lower TEPS-A scores (i.e., greater anticipatory anhedonia; r=-0.45, *p*=0.04), and lower TEPS-C scores (i.e., greater consummatory anhedonia; r=-0.62, *p*=0.003; Figure 5.10a), suggesting that more anhedonic patients learned faster about rewards. No other significant relationships with reward learning rate were observed (all absolute r<0.45, all *p*>0.05). No other parameters correlated significantly with any of the pre-specified symptom scales (all absolute r<0.38, all *p*>0.11). To better understand these effects, we explored the correlation between the reward learning parameter and performance on the task in terms of the number of points won. In patients, the number of points won was not significantly associated with reward learning rate (r=-0.18, *p*=0.43; Figure 5.10b), suggesting that higher reward learning rate does not significantly impair overall performance.

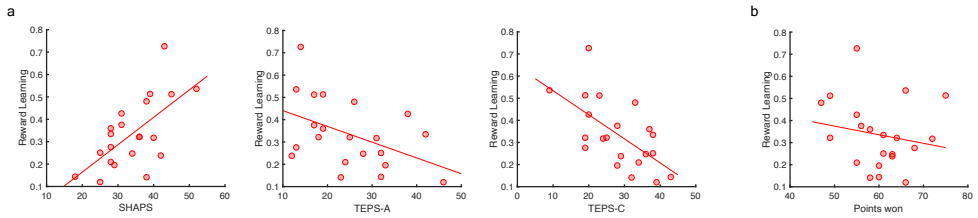

Figure 5.10 Correlations between reward learning rate, symptom scales and winnings on the four-armed bandit task in patients. Greater reward learning rate was associated with greater anhedonia across several anhedonia scales (a). Fewer points won on the task was associated with greater reward learning, but this association was not significant (*p*=0.43) (b). SHAPS: Snaith-Hamilton Pleasure Scale; TEPS-A: Temporal Experience of Pleasure Scale Anticipatory Subscale; TEPS-C: Temporal Experience of Pleasure Scale Consummatory Subscale.

5.4.3 Physical effort task: Case-control baseline comparison

There were significant main effects of effort ($F_{(1.37, 36.92)}$=40.28, *p*<0.001, η_p^2=0.60) and reward ($F_{(1.43, 38.62)}$=34.09, *p*<0.001, η_p^2=0.56) on the probability to accept an offer, with significant differences between all effort (all *p*<0.004) and reward (all *p*<0.036) levels. This was qualified by a significant effort-by-reward interaction ($F_{(3.44,92.85)}$=14.52, *p*<0.001, η_p^2=0.35; Figure 5.11a), such that increasing reward had a greater impact on choices at higher effort levels. As such, reward had a significant positive effect on acceptance rates and effort had a significant negative effect on behaviour (all *p*<0.001; Figure 5.11b). However, there was no significant effect of group or an interaction between group and acceptance rates (all *p*>0.55). The overall

probability to accept, reward sensitivity, and effort sensitivity did not significantly correlate with any symptom scales in patients (overall probability to accept: all absolute r-values<0.35, all *p*>0.16; reward sensitivity: absolute r-values<0.31, all *p*>0.23; effort sensitivity: absolute r-values<0.33, all *p*>0.20).

There was a significant effect of effort on success rates ($F_{(1.14,28.55)}$=11.94, *p*=0.001, η_p^2=0.32), but no significant difference interaction between effort and group on success rates ($F_{(3,75)}$=0.04, *p*=0.99, η_p^2=0.02). The significant effort effect on success rates was driven by significantly lower success rates on the 80% effort level (M=0.85, SEM=0.04) compared with 60% effort (M=0.97, SEM=0.02; *p*=0.001), 40% effort (M=0.99, SEM=0.01; *p*=0.002), and 20% effort (M=1.00, SEM=0.00; *p*=0.002), and lower success rates at the 60% relative to the 20% effort level (*p*=0.04). There was no significant correlation between the overall probability to accept (M=0.84, SEM=0.02) and overall success rates (M=0.96, SEM=0.01; r=-0.12, *p*=0.54, assessed across groups), nor between effort sensitivity in terms of acceptance rates (M=-0.90, SEM=0.16) and effort sensitivity in terms of success rates (M=-0.29, SEM=0.09; r=-0.02, *p*=0.93, linear contrasts of effort levels assessed across groups). In summary, success rates were generally high and did not seem to significantly influence decisions to accept an offer.

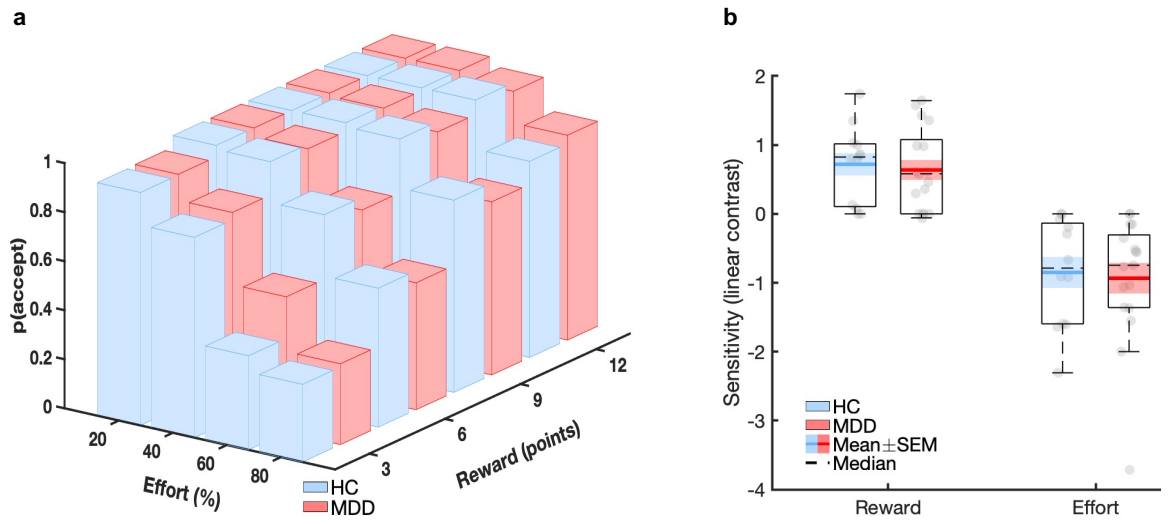

Figure 5.11 Case-control comparisons at baseline on the physical effort task. The probability to accept an offer based on reward and effort levels are presented for healthy controls (HC; N=12) and patients with major depressive disorder (MDD; N=17; a). Boxplots of reward and effort linear contrasts are displayed for healthy individuals and patients (b). Positive values indicate greater acceptance with increasing condition levels and negative values indicate lower acceptance with increasing effort levels. SEM: Standard error of the mean.

5.4.4 Clock task: Case-control baseline comparison

The main variable of interest in this task was the RT swing measure, indicating the degree of exploration in participants. Although patients had numerically lower scores on this measure (Figure 5.12a), this difference was not statistically significant ($t_{(29)}$=0.65, p=0.52). As expected, responses were slower in the no-go than in the go learning condition (main effect: $F_{(1,29)}$=33.23, p<0.001, η_p^2=53; Figure 5.12b). However, there were no significant effects involving group (main effect of group: $F_{(1,29)}$=0.02, p=0.90, η_p^2=0.001; group-by-learning interaction: $F_{(1,29)}$=2.87, p=0.10, η_p^2=0.09). There were also no significant correlations between any of the clock task measures and psychometric scales in patients: go-learning (absolute r-values<0.32, all p>0.20), no-go learning (absolute r-values<0.23, all p>0.35) and overall RT swing (absolute r-values<0.36, all p>0.15).

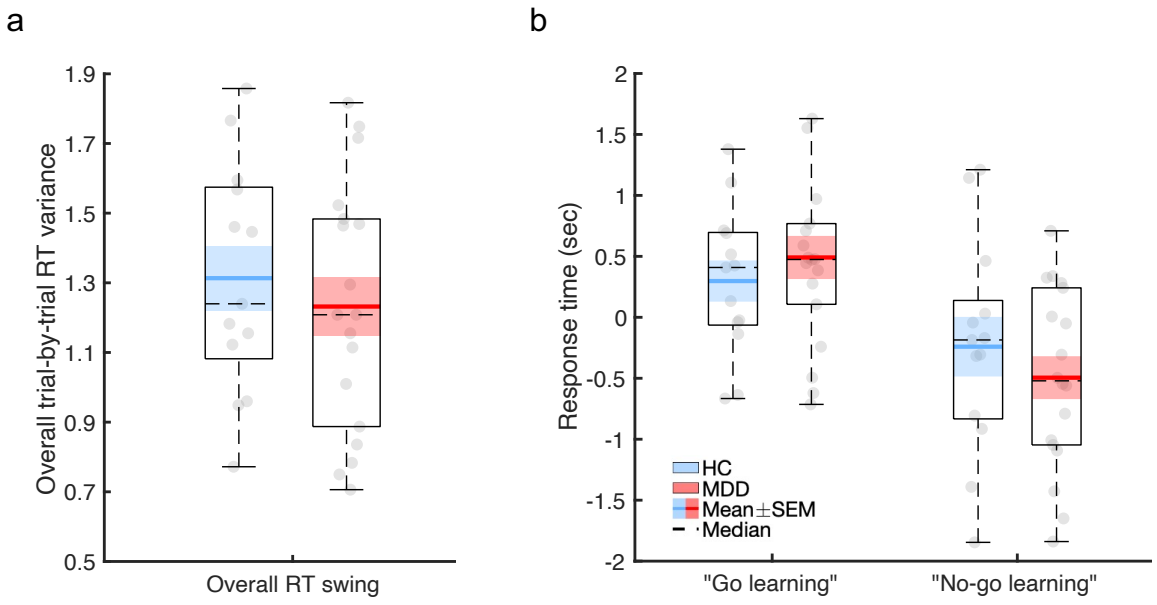

Figure 5.12 Case-control comparisons at baseline on the clock task. The overall RT swing, a proxy of exploration, is displayed for healthy controls (HC; N=13) and patients with major depressive disorder (MDD; N=18; a). Response times for go (speeding of responses; decreasing expected value – DEV – condition minus the constant expected value – CEV – condition) and no-go (slowing of responses; increasing expected value – IEV – condition minus the CEV condition) are presented for both groups (b). SEM: Standard error of the mean.

5.4.5 Reward/punishment bias task: Case-control baseline comparison

There was no significant main effect of valence on response bias ($F_{(1,30)}$=1.32, p=0.26, η_p^2=0.04). In contrast to predictions however, response bias valence did not significantly differ between healthy controls and patients (response bias valence x group interaction: $F_{(1,30)}$=0.81, p=0.38, η_p^2=0.03; Figure 5.13a), and the groups did not differ significantly in their overall response bias ($F_{(1,30)}$=0.002, p=0.97, η_p^2<0.001). However, one-sample t-tests (test value=0) did not reveal an expected significant reward response bias ($t_{(31)}$=0.40, p=0.69, Cohen's d=0.07), while a significant response bias was evident in the punishment condition ($t_{(31)}$=2.44, p=0.01, Cohen's d=0.43). There was no significant interaction between group and valence (reward/punishment) condition on task discriminability ($F_{(1,30)}$=1.82, p=0.19, η_p^2=0.06; Figure 5.13b) or any group ($F_{(1,30)}$=0.90, p=0.35, η_p^2=0.03) or valence effects ($F_{(1,30)}$=0.49, p=0.49, η_p^2=0.02). There were no significant correlations between response bias and psychometric scale in patients (reward: all absolute r-values<0.30, all p>0.20; punishment: all absolute r-values<0.27, all p>0.25). Task discriminability on reward trials was negatively correlated with BDI scores in patients (r=-0.58,

p=0.007), but did not significantly correlate with any other scales (all absolute r-values<0.38, all *p*>0.12). Task discriminability on punishment trials showed a similar relationship with BDI in patients, although this narrowly missed statistical significance (r=-0.41, *p*=0.07). No other correlations approached significance (all absolute r-values<0.32, all *p*>0.19).

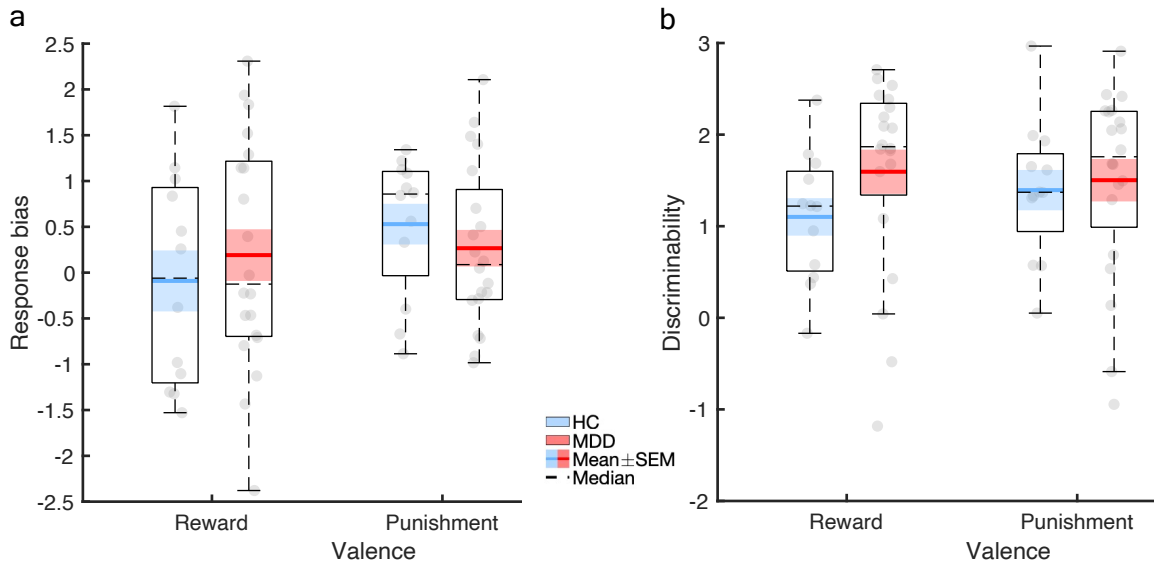

Figure 5.13 Case-control comparisons at baseline on the reward/punishment bias task. Boxplots of response bias for the reward and punishment conditions in healthy controls (HC; N=12) and patients with major depressive disorder (MDD; N=20; a) Positive values indicate a preference for the stimuli that was rewarded more often/punished more often, as correct responses on these trials would lead to more rewards/avoiding more losses. Boxplots of task discriminability for the reward and punishment condition in HCs and patients (b). SEM: Standard error of the mean.

5.4.6 Ketamine effects: Unblinding

Since unblinding was not possible at the time of writing, CADSS scores were examined 40 minutes post-infusion. For all individuals except one (patient 7, for whom CADSS scores remained the same under placebo and ketamine), CADSS scores were numerically higher under ketamine 40 minutes post-infusion (Figure 5.14). This offers reassurance that the current unblinding is correct. However, since official unblinding was not possible – all following ketamine effects are only presumed and labelled as such.

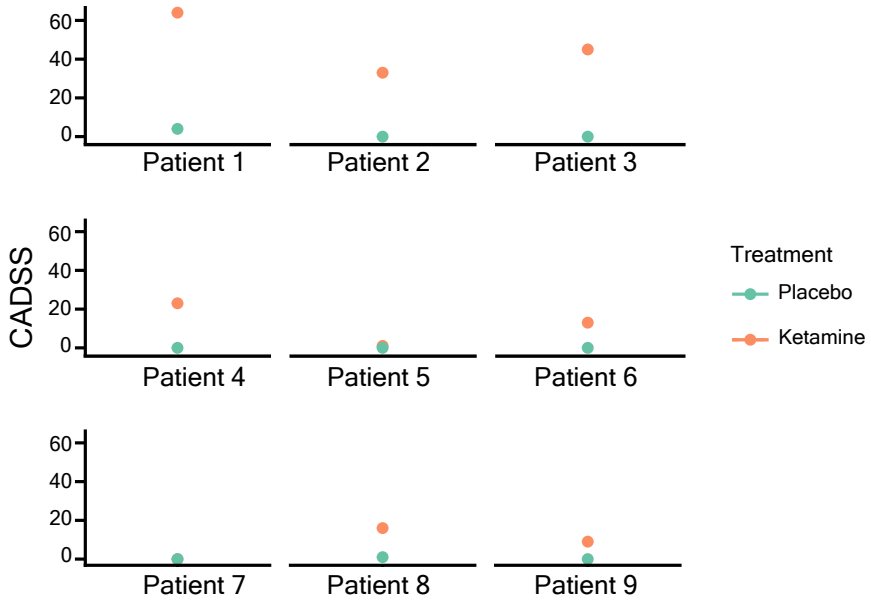

Figure 5.14 Post-infusion scores on the Clinician-Administered Dissociative States Scale (CADSS). Data is provided for all nine patients completing both placebo and ketamine infusions, with CADSS scores presented 40-minutes post-infusion. Greater scores indicate greater dissociative symptoms.

5.4.7 Symptom scales: Presumed ketamine effects

Figure 5.15a shows the effect of presumed ketamine, versus placebo, on MADRS raw scores over time (not showing adjusted values controlling for baseline scores as assessed in the model). All presented effect sizes (d_z scores) here are derived from simple paired t-tests (non-hierarchical). Although MADRS scores were numerically lower on average post-ketamine (M=25.75, SEM=0.82) than post-placebo (M=27.43, SEM=0.82), this difference narrowly missed significance (main effect of treatment: $F_{(1,90.98)}$=2.89, p=0.09). MADRS scores did not significantly differ over time between presumed ketamine and placebo infusions either (treatment-by-time interaction: $F_{(5,\ 80.26)}$=0.78, p=0.57). There was also no significant effect of presumed ketamine on day-one MADRS scores ($F_{(1,82.415)}$=1.81, p=0.18, d_z=0.27). SHAPS scores were numerically reduced on average post- presumed ketamine, although this difference narrowly missed significance (main effect of treatment: $F_{(1,\ 88)}$=3.03, p=0.085; placebo: M=38.17, SEM=2.30; ketamine: M=37.22, SEM=2.30), but this did not differ over time (treatment-by-time interaction: $F_{(5,\ 88)}$=0.73, p=0.61; Figure 5.15b). The effect of presumed ketamine on SHAPS scores was largest on day one, and again this effect narrowly missed

significance ($F_{(1,88)}$=3.39, p=0.07; d_z=0.48). Anticipatory anhedonia (TEPS-A) was not significantly different between presumed placebo and ketamine overall ($F_{(1, 88)}$=2.70, p=0.10; placebo: M=20.13, SEM=3.53; ketamine: M=21.06, SEM=3.53), and there was no significant differential presumed ketamine effect over time (treatment-by-time interaction: $F_{(5, 88)}$=1.29, p=0.27; Figure 5.15c). At one day post-infusion anticipatory anhedonia was lower post- presumed ketamine, although this effect narrowly missed significance ($F_{(1,88)}$=2.86, p=0.09, d_z=0.61). Presumed ketamine did however significantly decrease consummatory anhedonia (TEPS-C, indicated by lower scores) overall ($F_{(1, 88)}$=19.0, p<0.001; placebo: M=24.69, SEM=2.80; ketamine: M=26.82, SEM=2.80). There was also a main effect of time ($F_{(5, 88)}$=4.50, p=0.001) with scores being greater (lower anhedonia) closer to the infusion time (all p<0.02). However, the treatment-by-time interaction was non-significant ($F_{(5, 88)}$=0.47, p=0.78, Figure 5.15d), and there was no significant effect of presumed ketamine one day post-infusion ($F_{(1,88)}$=2.50, p=0.12, d_z=0.49). Finally, there were no significant effects of presumed ketamine on any of the secondary scales of interest, for which data were only available on the day of testing (day one; Table 5.3; Figure 5.15e).

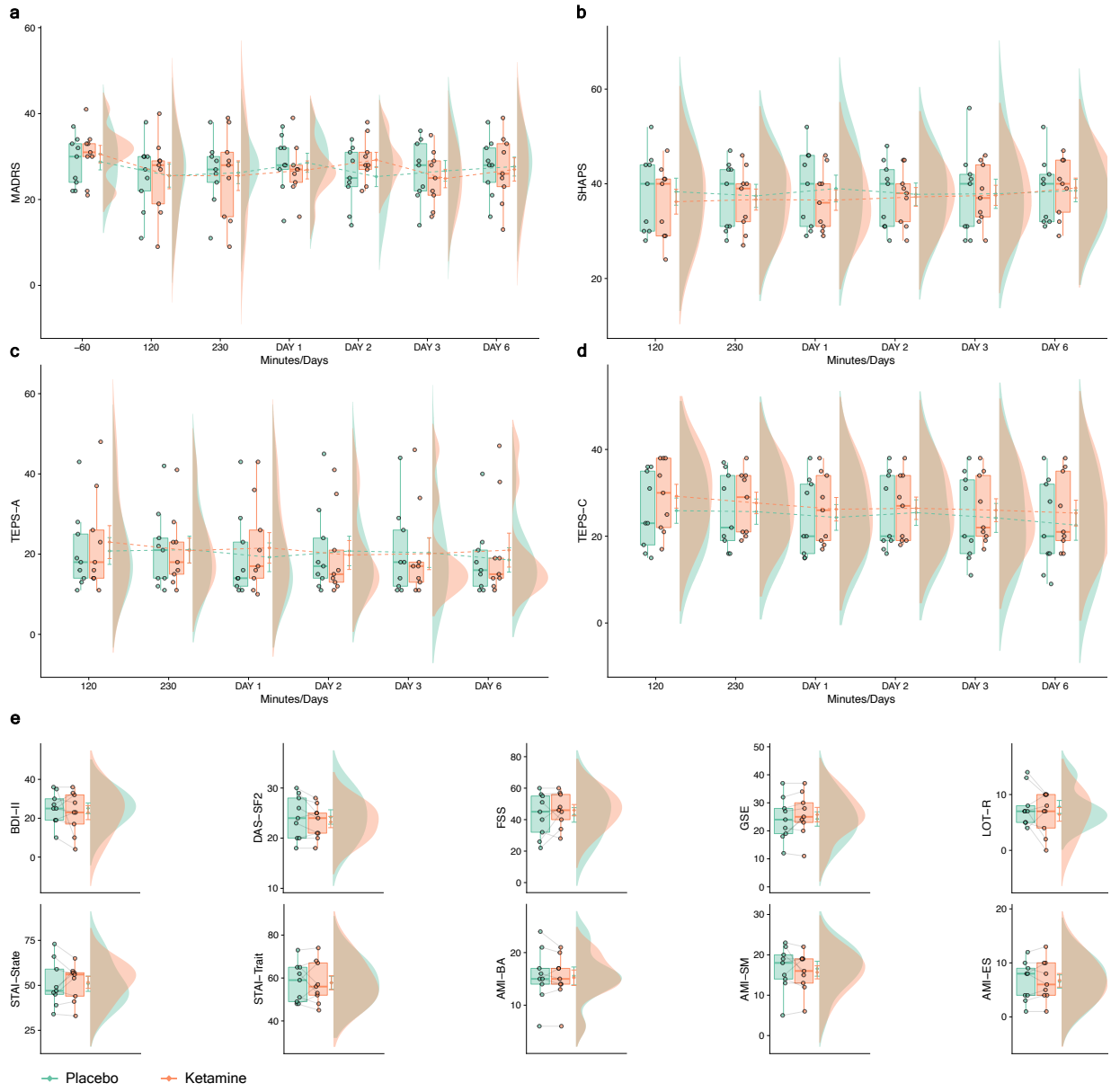

Figure 5.15 Presumed ketamine effects on symptom scales. All figures show boxplots with overlaid individual data points, data distributions and mean±standard error of the mean. Changes in Montgomery-Åsberg Depression Rating Scale (MADRS; a), Snaith-Hamilton Pleasure Scale (SHAPS; b), Temporal Experience of Pleasure Scale Anticipatory Subscale (TEPS-A; c), and Temporal Experience of Pleasure Scale Consummatory Subscale (TEPS-C; d) following ketamine and placebo over time. Changes in secondary scale one day following ketamine and placebo (e). Higher scores indicate greater severity on the symptom dimension measured by all scales, except the TEPS, GSE and LOT-R, where lower scores indicate greater severity. Post-ketamine changes for all scales were in the expected direction (lower symptom severity) except for the FSS, LOT-R, STAI-State and AMI-ES. BDI-II: Beck Depression Inventory Second Edition; DAS-SF2: Dysfunctional Attitude Scale Short Form 2; FSS: Fatigue Severity Scale; GSE: General Self-Efficacy Scale; LOT-R: Life Orientation Test-Revised; STAI-State: State-Trait Anxiety Inventory-State Subscale; STAI-Trait: State-Trait Anxiety Inventory-Trait Subscale; AMI-BA: Apathy Motivation Index Behavioural Activation; AMI-SM: Apathy Motivation Index Social Motivation; AMI-ES: Apathy Motivation Index Emotional Sensitivity.

Scale	*t*-value	*p*-value	Cohen's d_z
BDI-II	0.70	0.50	+0.23
DAS-SF2	1.81	0.12	+0.60
FSS	1.02	0.34	-0.34
GSE	1.67	0.13	-0.56
LOT-R	1.32	0.23	+0.44
STAI-State	0.31	0.76	-0.10
STAI-Trait	0.00	1.00	+0.00
AMI-BA	0.71	0.50	+0.24
AMI-SM	0.84	0.43	+0.28
AMI-ES	0.55	0.59	-0.19

Table 5.3 Presumed ketamine effects on secondary scales of interest on the day of testing (Day 1) for nine treatment-resistant depressed patients. Effects are presented for the presumed placebo minus ketamine sessions. Higher scores indicate greater severity on the symptom dimension measured by all scales, except the GSE and LOT-R, where lower scores indicate greater severity. Post-ketamine changes for all scales were in the expected direction (lower symptom severity) except for the FSS, LOT-R, STAI-State and AMI-ES. BDI-II: Beck Depression Inventory Second Edition; DAS-SF2: Dysfunctional Attitude Scale Short Form 2; FSS: Fatigue Severity Scale; GSE: General Self-Efficacy Scale; LOT-R: Life Orientation Test-Revised; STAI-State: State-Trait Anxiety Inventory-State Subscale; STAI-Trait: State-Trait Anxiety Inventory-Trait Subscale; AMI-BA: Apathy Motivation Index Behavioural Activation; AMI-SM: Apathy Motivation Index Social Motivation; AMI-ES: Apathy Motivation Index Emotional Sensitivity.

5.4.8 Four-armed bandit task: Presumed ketamine effects

5.4.8.1 Model-agnostic measures

Consistent with data collected at baseline, participants' choices were modulated by outcome type ($F_{(2,10.05)}$=16.44, p=0.002, η_p^2=0.67). They were more likely to repeat an option if it was rewarded compared with receiving no feedback (p=0.01) or punishment (p<0.001), and less likely to repeat a choice if it was punished compared with no feedback (p=0.01). However presumed ketamine did not modulate the overall probability to stay ($F_{(1,8)}$=0.15, p=0.71, η_p^2=0.02), nor did it modulate the probability to stay after a specific outcome type ($F_{(2,10.74)}$=0.86, p=0.40, η_p^2=0.10; Figure 5.16).

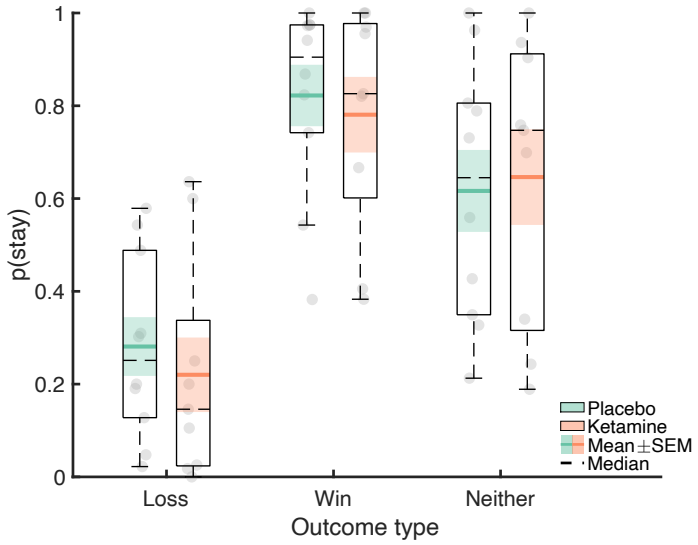

Figure 5.16 Post-infusion task performance on the four-armed bandit task (model-agonist measures). Boxplots with individual datapoints displaying the probability to stay after a certain outcome one day post-presumed ketamine and post-placebo infusions in treatment-resistant patients. SEM: Standard error of the mean.

5.4.8.2 Computational model

Presumed ketamine significantly increased punishment learning rate compared with placebo ($t(8)=2.55$, $p=0.03$, $d_z=0.85$). There were no other significant differences between presumed ketamine and placebo on RL parameters (reward learning: $t(8)=0.38$, $p=0.71$, $d_z=0.13$; reward sensitivity: $t(8)=0.28$, $p=0.79$, $d_z=0.09$; punishment sensitivity $t(8)=0.02$, $p=0.98$, $d_z=0.01$; Figure 5.17).

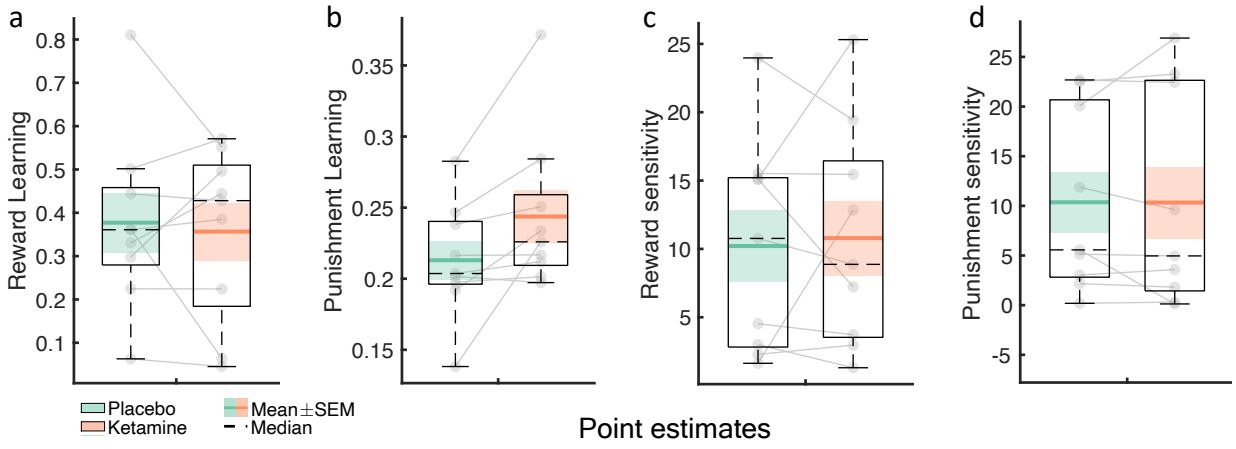

Figure 5.17 Presumed ketamine effects on the four-armed bandit reinforcement learning model in treatment-resistant depressed patients. Mean posterior point estimates of subject-specific reward learning (a), punishment learning (b), reward sensitivity (c) and punishment sensitivity (d) parameters are presented for presumed ketamine and placebo. SEM: Standard error of the mean.

To further understand the presumed post-ketamine increase in punishment learning, the difference in this parameter between sessions (ketamine minus placebo) was correlated with the difference in total number of points lost between sessions (ketamine minus placebo). A higher number of punishment outcomes experienced post-presumed ketamine was associated with higher punishment learning rate post-presumed ketamine (r=0.68, p=0.045; Figure 5.18). The number of points won on this task was however significantly greater in the presumed ketamine than placebo condition (placebo wins: M=52.89, SEM=1.68; ketamine wins: M=59.67, SEM=2.74; t(8)=2.88, p=0.02, d_z=0.96), while the number of points lost was very similar between sessions (placebo losses: M=59.78, SEM=1.20; ketamine losses: M=59.67, SEM=2.00; t(8)=0.06, p=0.96, d_z=0.02).

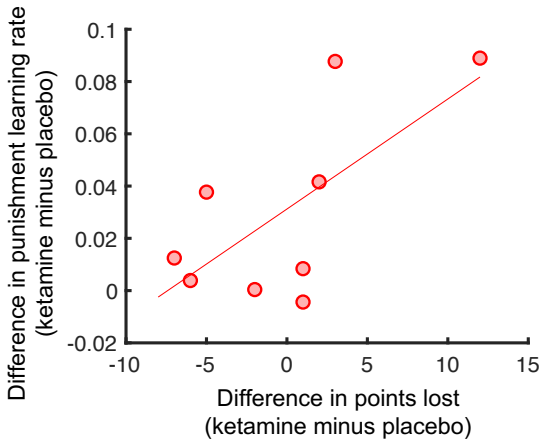

Figure 5.18 Correlation between the difference in post-infusion punishment learning rate and number of punishments experienced on the four-armed bandit task. Positive numbers indicate increases under presumed ketamine compared with placebo.

5.4.9 Physical effort task: Presumed ketamine effects

Both reward and effort exerted a significant effect on behaviour, increasing the probability to accept an offer with increasing reward, and reducing the probability to accept an offer with increasing effort levels (all $p<0.02$). Presumed ketamine did not modulate the propensity to accept offers (reward sensitivity: $t(8)=0.91$, $p=0.39$, $d_z=0.30$; effort sensitivity: $t(8)=0.70$, $p=0.50$, $d_z=0.23$; overall probability to accept offer: $t(9)=0.68$, $p=0.52$, $d_z=0.23$; Figure 5.19a-b). No significant effects of effort on success rates or effort-by-treatment effects were observed (all $p>0.22$; success rates per effort level: 80% M=0.94, SEM=0.04; 60% M=0.98, SEM=0.01; 40% M=0.99, SEM=0.01; 20% M=0.99, SEM=0.01; N=7 for this analysis as two subjects did not accept any trials at a certain effort level).

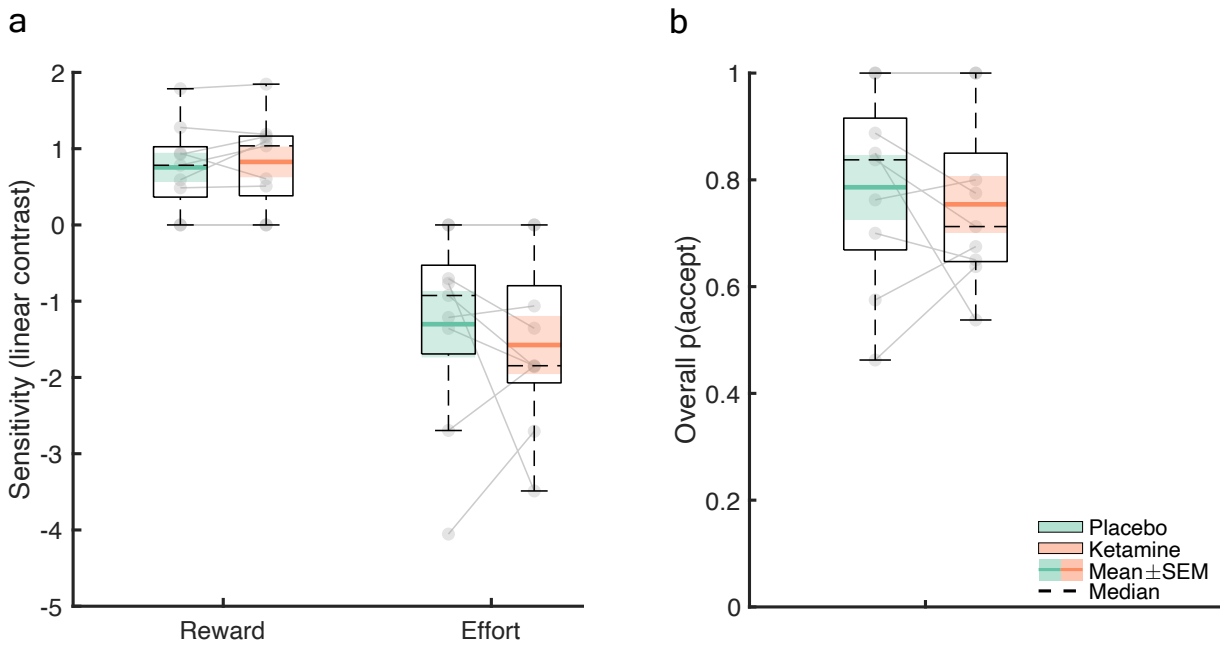

Figure 5.19 Post-infusion task performance on the physical effort task in treatment-resistant depressed patients. Boxplots with individual datapoints displaying reward and effort linear contrasts post-presumed ketamine and post-placebo sessions (a). Positive values indicate greater acceptance levels with increasing condition levels and negative values indicate lower acceptance levels with increasing condition levels. The effect of presumed ketamine versus placebo on the overall probability to accept an offer (b). SEM: Standard error of the mean.

5.4.10 Clock task: Presumed ketamine effects

Participants showed the expected go and no-go learning patterns on the clock task (main effect of condition: $F(1,8)=13.11$, $p=0.007$, $\eta_p^2=0.62$), producing faster response times in go (difference in response times between the CEV and DEV condition) than no-go (difference in response times between the CEV and IED condition) learning conditions.

Interestingly, presumed ketamine significantly increased RT swings ($t(8)=5.17$, $p<0.001$, $d_z=1.72$; Figure 5.20a). It is here assumed that RT swings are related to uncertainty-driven exploration, which potentially might facilitate performance over time. To examine this assumption, we explored the relationship between overall RT swings and rewards won post-infusion. Although there was a positive relationship between points won and increases in RT swings post-presumed ketamine, relative to post-placebo, this relationship was not significant (r=0.12, $p=0.76$). Presumed ketamine did not modulate go vs no-go learning (treatment-by-learning

interaction: $F_{(1,8)}$=0.19, p=0.68, η_p^2=0.02; Figure 5.20b), nor did it have an overall effect on response times (main effect of treatment: $F_{(1,8)}$=0.25, p=0.63, η_p^2=0.03).

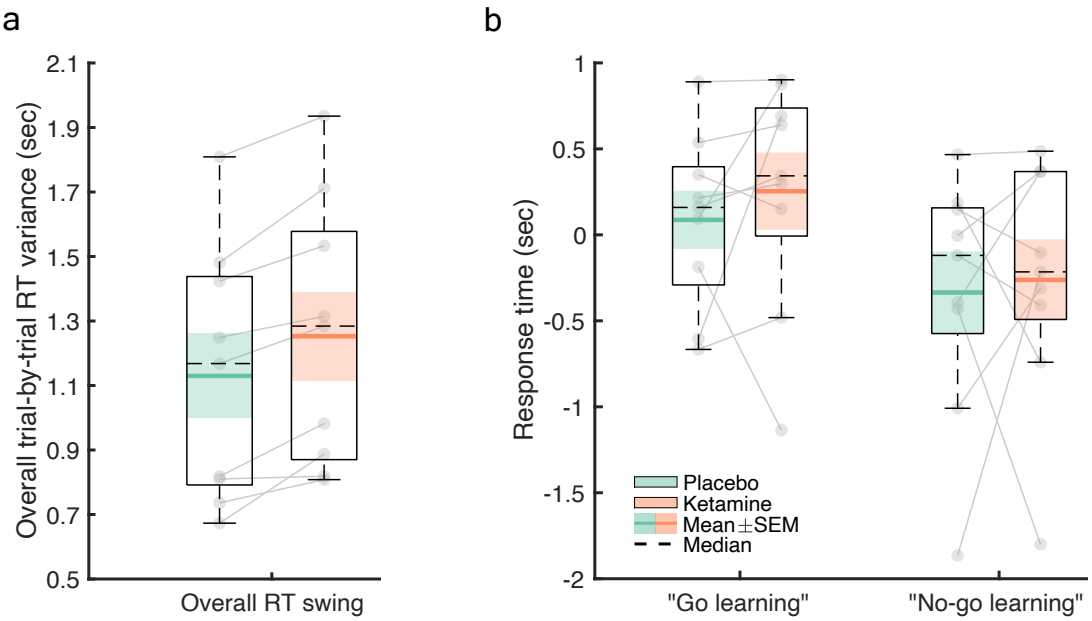

Figure 5.20 Post-infusion performance on the clock task in treatment-resistant depressed patients. Boxplots with individual datapoints displaying response times for "go learning" (speeding of responses: the constant expected value condition minus the decreasing expected value condition) and "no-go learning" (slowing of responses: the constant expected value condition minus the increasing expected value condition) trials (a), and the overall RT swing, a proxy of exploration (b). Greater RT swing scores indicate greater exploration. SEM: Standard error of the mean.

5.4.11 Reward/punishment bias task: Presumed ketamine effects

Presumed ketamine did not significantly impact response bias compared with placebo (main effect of treatment: $F_{(1,6)}$=1.36, p=0.29, η_p^2=0.19; treatment-by-valence interaction: $F_{(1,6)}$=1.30, p=0.30, η_p^2=0.18; Figure 5.21a). Response bias was also not significantly different between the reward and punishment conditions ($F_{(1,6)}$=0.67, p=0.44, η_p^2=0.10). Similarly, there were no significant effects of presumed ketamine on task discriminability (treatment main effect: $F_{(1,6)}$=1.24, p=0.31, η_p^2=0.17; treatment-by-valence condition interaction: $F_{(1,6)}$=0.003, p=0.96, η_p^2<0.001; Figure 5.21b). Discriminability did not significantly differ between the reward and punishment conditions either ($F_{(1,6)}$=0.81, p=0.40, η_p^2=0.12).

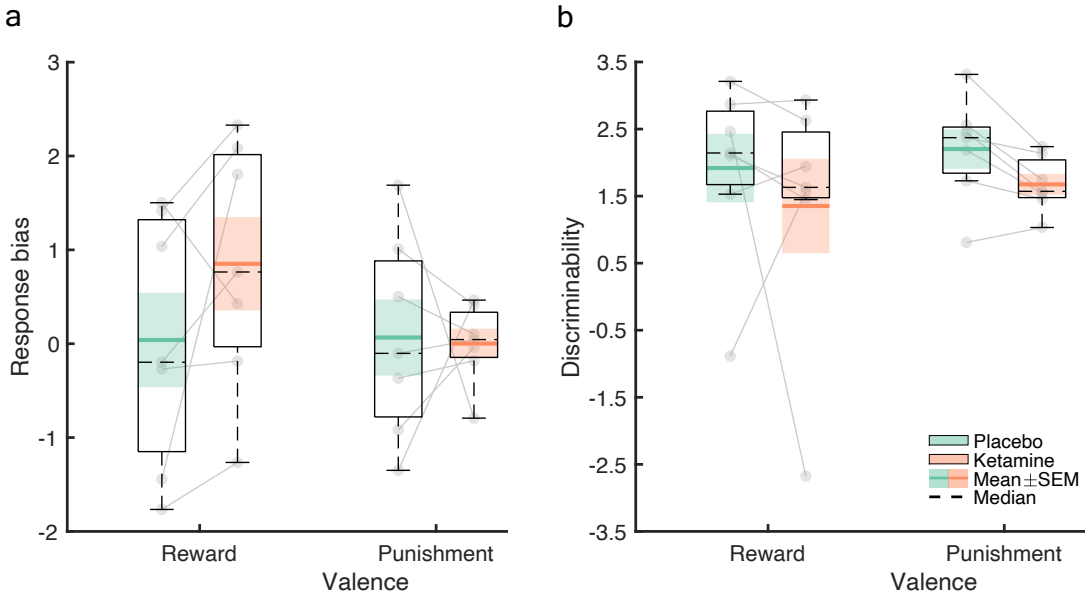

Figure 5.21 Post-infusion task performance on the reward/punishment bias task in treatment-resistant depressed patients (N=7). Boxplots of response bias for the reward and punishment conditions (a). Positive values indicate a preference for the stimuli that was rewarded more often/punished more often, as correct responses on these trials would lead to greater rewards/avoiding more losses. Boxplots of task discriminability for the reward and punishment condition (b). Greater values indicate greater discriminability between the two task stimuli, long and short bars (i.e., the task is easier). SEM: Standard error of the mean.

5.5 Discussion

The aim of this study was to understand the mechanisms underlying ketamine's anti-anhedonic effects. In particular, the current chapter focused on understanding this from the perspective of changes in reward and punishment processing, drawing on a rich literature that has implicated these as key components in anhedonic symptomatology (Admon & Pizzagalli, 2015; Bekhbat et al., 2022; Bishop & Gagne, 2018; Borsini et al., 2020; Cooper et al., 2018; Der-Avakian & Markou, 2012; Der-Avakian & Pizzagalli, 2018; Eshel & Roiser, 2010; Felger & Treadway, 2017; Husain & Roiser, 2018; Huys et al., 2021; Kieslich et al., 2022; Lucido et al., 2021; Pizzagalli, 2014; Rizvi et al., 2016; Rømer Thomsen et al., 2015; Treadway, 2016; Treadway et al., 2019; Treadway & Pizzagalli, 2014; Treadway & Zald, 2011, 2013; Wang et al., 2021; Zald & Treadway, 2017; Zhang et al., 2016). Notably, presumed ketamine increased exploratory behaviours, as assessed with the clock task, with this pattern observed in every individual. In addition, presumed ketamine increased punishment learning rates, with preliminary analyses suggesting that this may have been associated with worse task performance. However, no significant effects of presumed ketamine on any other motivational processes emerged, including reward learning or sensitivity, punishment sensitivity, willingness to exert physical effort, or response biases to either rewards or punishments. However, these conclusions are strongly limited by the small sample size. Indeed, although moderate-to-large decreases in symptoms were observed following presumed ketamine (effect sizes of d_z up to 0.61 one day post-infusion), none of these achieved statistical significance.

5.5.1 Clock task

The increase in RT swing following presumed ketamine, indexing exploratory behaviours, is consistent with the study hypotheses. The effect size observed was extremely large, and due to the small sample size is likely an over-estimation. Although no significant differences were detected for the case-control comparison, as expected exploratory behaviours were numerically lower in patients. Adaptive behaviour requires striking a balance between exploiting, i.e., choosing the option with the highest expected value given what you know, and exploring options for potential better outcomes. Exploratory behaviours are however not

always adaptive. Human behaviour comprises at least two types of exploratory behaviours: random and directed; directed exploration guides choices toward options with greater relative uncertainty about reward outcomes (information-gathering-based exploration) (Gershman, 2018; Wilson et al., 2021). Previous studies suggest that individuals with MDD and anhedonia might show greater choice variability (Robinson & Chase, 2017) , which has been presumed to reflect random exploration. However, few previous studies have explicitly examined goal-directed exploration in MDD. One advantage of the clock task is that previous studies suggest that the exploratory behaviour, as measured with RT swings, do indicate uncertainty-driven exploration more than random exploration (Badre et al., 2012; Cavanagh et al., 2012; Frank et al., 2009; Kayser et al., 2015; Morris, Baek, et al., 2016; Strauss et al., 2011). These results thus extend earlier findings showing lower uncertainty-driven exploration in individuals with greater anhedonia (Strauss et al., 2011), and suggest that this might be one possible cognitive process involved in the antidepressant effects of ketamine.

The above discussion assumes that the RT swing measure represents goal-directed exploration, as previous studies have found strong positive correlations between an uncertainty-driven exploration parameter and RT swings (Badre et al., 2012; Frank et al., 2009; Strauss et al., 2011), however some studies have recently cast doubt on this; these have suggested that RT swings instead represent stochastic exploration that does not facilitate behaviour (Hallquist & Dombrovski, 2019). If this explanation is correct, higher RT swings would potentially lead to suboptimal behaviours. However, no presumed ketamine effects were observed on general performance on the clock task (go/no-go learning). One possible explanation for this is that only the overall RT swing measure showed good reliability, as identified in Chapter 2. In addition, we note that overall RT swings were positively, but not significantly, correlated with the number of points won on this task. These would be in line with a directed, rather than random exploration interpretation, arguing against a pure random exploration account of RT swings. However, it must be recognised that adaptive exploratory choices may follow an inverted U-shaped trajectory (Addicott et al., 2017), thus the relationship between overall RT swings and points won might be more complicated than can be assessed in this study. Ultimately, a computational

model is required to clarify the precise nature of the current exploration measure. It will additionally be important to examine how ketamine affects random and directed exploration, which can be assessed using tasks that specifically distinguish between these two (Gershman, 2018; Wilson et al., 2014)

Despite the above caveats, our finding of a specific presumed ketamine effect on exploratory behaviours is intriguing, and to our knowledge, no previous studies have examined this. Of note, it has been suggested that exploration may play a role in curiosity-driven behaviours and interest (Berlyne, 1966; Geana et al., 2016; Gottlieb et al., 2013; Kidd & Hayden, 2015; Peterson & Verstynen, 2022; Schwartenbeck et al., 2019). Thus, one interpretation is that ketamine may facilitate the need to explore and be curious about the world, which is more closely related to intrinsic motivation; consistent with this, a lack of curiosity has previously been described in anhedonia (Watson et al., 2020). Thus, in curiosity-driven exploration, information-seeking is rewarding and a goal in and of itself, while goal-directed exploration can also be an intermediate step toward achieving a goal, such as maximising rewards. It has also recently been suggested that confidence (here meaning uncertainty in an individual's representation of value beliefs, which is measured through explicit confidence judgments) may influence the balance between exploitation and exploration, with greater metacognitive insight being associated with better tracking of uncertainty (Boldt et al., 2019). Interestingly, one previous study in healthy individuals suggests that ketamine might modulate a 'meta-level' confidence-related parameter, which in turn influences choice temperature (putatively reflecting random exploration) and learning rate parameters on a reversal learning task in healthy individuals (Vinckier et al., 2016). Thus, an interesting extension of the current findings would be to examine whether ketamine alters the precision of beliefs about the state of the world, and/or on the ability to use confidence information to inform uncertainty-driven exploration.

5.5.2 Four-armed bandit task

In contrast with our predictions however, there was no clear evidence for presumed ketamine affecting reward learning or sensitivity on the four-armed bandit task. Indeed, contrary to our

predictions based on case-control contrasts (Halahakoon et al., 2020), patients with greater anhedonia symptoms displayed greater reward learning. Although puzzling at a first glance, lower reward learning rates were associated with greater accumulated rewards, suggesting that a high reward learning rate is not necessarily adaptive on this task. However, this effect was weak and, importantly, not significant. Thus, the greater reward learning rate in more anhedonic patients is currently unclear as it did not significantly impair overall performance. Nevertheless, a possible interpretation might lie in how reward learning rates are calculated, where a higher learning rate could be due to learning about good things, but also due to learning from omissions of rewards — a subtle but important distinction. In this case, it is possible that the higher reward learning rate in more severe anhedonic patients may stem from learning more from omissions of rewards. However, this finding contrasts with previous studies suggesting that reward sensitivity, but not reward learning rates are lower in anhedonia (Huys et al., 2013) as well as previous studies indicating lower reward learning rates in depression (Admon et al., 2017; Chase et al., 2010; Chen et al., 2015; Gradin et al., 2011; Greenberg et al., 2015; Halahakoon et al., 2020; Kumar et al., 2018; Kumar et al., 2008; Reinen et al., 2021; Robinson & Chase, 2017; Robinson et al., 2012; Vrieze et al., 2013, Brown et al 2021). Thus, the identified relationship should be considered preliminary and requires replication.

Interestingly, presumed ketamine did not significantly modulate reward learning rate, although again it is important to acknowledge the low power of the study. In contrast, punishment learning rates were increased post-presumed ketamine, again contrary to initial predictions. Previous studies suggest that patients with mood and anxiety symptoms have an elevated punishment learning rate, reflecting faster learning about punishments (Aylward et al., 2019), with a recent meta-analysis suggesting that patients with mood and anxiety disorder show elevated punishment learning rates across tasks (Pike & Robinson, 2022). The presumed ketamine-induced increase in punishment learning rate in the current study was further associated with losing more points, suggesting that this increase was not necessarily adaptive. However, we also observed that presumed ketamine facilitated overall task performance as demonstrated by significantly more points won post-presumed ketamine than post-placebo

(although surprisingly this effect was not reflected in any model-based or model-agnostic measures), while no such infusion-difference was observed for the number of points lost. One possibility is that presumed ketamine's effects on points won compared with lost are not related since the task is designed to assess the independent effect of rewards and punishments. However, considering the small range in punishment learning rates as compared with the reward learning rates (see Figure 5.9 and Figure 5.17), the low statistical power and that this effect was not *a priori* hypothesised, this finding should be considered preliminary and requires replication.

Only one previous study has examined ketamine's effects on reinforcement learning in TRD patients. Similar to the present results, this previous study did not find an effect of ketamine on reward learning on a simple reinforcement learning task (Lally, 2015; Mkrtchian et al., 2019). Acute ketamine (1h post ketamine administration) has been shown to impair general RL on a probabilistic reversal learning task assessing only reward learning in rodents (Wilkinson et al., 2020). However, considering that ketamine may have differential effects in healthy and depressed populations (as discussed in Chapter 4) and the higher dosages in the rodent study (1, 3, and 10mg/kg), coupled with the different timepoints tested (1 hour in rodents, versus one-day post-infusion here), these results are difficult to compare. In particular the changes observed in rodents might reflect general cognitive impairment unrelated to antidepressant effects as impairments were most prominent on the highest ketamine dose (Wilkinson et al., 2020).

5.5.3 Reward/punishment bias task

Although past studies suggest mixed evidence for the association between reward sensitivity and/or learning with anhedonia, it has been much more consistently reported that individuals with depression and anhedonia show lower reward bias (Halahakoon et al., 2020). Indeed, in a large meta-analysis examining differences in various aspects of reward-processing between depressed and healthy individuals, the most prominent effect emerged for a reward response bias impairment in the PRT (Halahakoon et al., 2020). Surprisingly, the current study did not

find a similar effect. However, the current task was substantially modified to incorporate a punishment condition to examine the specificity of the valence effect. Reward and punishment conditions were presented in an interleaved manner, potentially leading to greater working memory demands than previous versions. Although the learning component was removed to make the task easier (by instructing participants), it is quite possible that the addition of the punishment condition altered responses observed on this task. Indeed, neither patients nor HCs exhibited the expected reward response bias, although a punishment response bias was evident. Thus, introducing the punishment condition may have inadvertently interfered with the reward condition, such that the punishment condition was more salient. Future studies should use separate blocks of each valence condition to remedy this.

Lower ability to perceptually distinguish between the short and long bars (discriminability) on this task was however associated with greater depression severity. This contrasts with previous studies reporting altered response bias but intact task discriminability in depression on the original task (Huys et al., 2013). This finding might also be related to the novel task design, which might have promoted lapses in attention due to greater complexity, or the more severe patient group. Notably, depression is associated with cognitive impairments such as difficulty concentrating (American Psychiatric Association, 2013), potentially explaining this finding.

Interestingly, a recent study in marmoset monkeys demonstrated an increase in reward response bias post-ketamine (Wooldridge et al., 2020). However, this study used considerably higher doses of ketamine (1-10mg/kg) than in the current study and impairments were observed at the highest dosage. Thus, it is unclear if similar effects would be observable at the antidepressant dose of 0.5mg/kg in TRD patients. Although the current study did find a numerical increase of reward response bias under presumed ketamine, compared with placebo, consistent with the hypotheses, this effect was not significant and in any case is difficult to interpret in light of the absence of a reward bias overall. It is speculated that the current task design may have hampered our ability to fully examine the effect of ketamine on reward

response bias. Considering the positive findings from the non-human primate study, future ketamine studies in TRD patients on the PRT are warranted.

5.5.4 Physical effort task

In contrast to our predictions and previous case-control studies (Husain & Roiser, 2018; Huys et al., 2021; Treadway & Zald, 2013), no differences were observed between patients and healthy individuals on the physical effort task as measured by either overall probability to accept an offer, or effort sensitivity. Reward sensitivity did not differ significantly between groups either. Although surprising, we note that at least one previous study also failed to detect an impairment in effort-based decision making in patients (Lally, 2015); although, like the current study, this previous study was limited by sample size. It is also possible that participants were performing at ceiling levels in this task, as the overall probability to accept an offer was over 80%, with four individuals accepting all offers, and eight individuals accepting over 90% (across patients and healthy individuals). Thus, the current task version may have not sufficiently sensitive and may require additional effort/reward levels to increase sensitivity.

Presumed ketamine did not modulate any measures on the physical effort task either. We noted significant small-to-medium practice effects on the effort sensitivity and overall probability to accept measures on a similar effort task in Chapter 2. Considering that the anti-anhedonic effect was relatively modest in the current sample (largest effect size on day 1 found for anticipatory anhedonia d_z=0.61) compared with previous reports (Lally et al., 2014), it is possible that this may have prevented us from detecting a ketamine effect on physical effort. Although contrary to our initial hypotheses, this is consistent with one previous study using a conceptually similar task (Lally, 2015). This study employed the EEfRT, in which participants choose between an easy or hard physical effort challenge with the hard option varying in the number of rewards on offer (Treadway et al., 2009). Another study using this task in rodents similarly did not find an effect of acute ketamine (1 hour post-ketamine) on effort-based decision making (Griesius et al., 2020). Instead, the willingness to exert effort for higher rewards was if anything reduced under ketamine. However, this was most noticeable at the

highest dose of ketamine (10mg/kg), while a much lower dose is typical for antidepressant studies in humans (0.5mg/kg), suggesting that the impairment may be unrelated to any antidepressant effects, which were not examined in this rodent study.

Although the current study employed an effort-based task to address some of the limitations of the previously used EEfRT in ketamine studies, such as insufficient orthogonalizing of reward and effort levels, and the complication of modulating reward probability, the current study also did not find a significant ketamine effect on effort decisions. Thus, considering the similar pattern of results across studies, while limited by low statistical power, these results tentatively do not support the hypothesis that willingness to exert physical effect is involved in ketamine's antidepressant effects.

5.5.5 Limitations

Several limitations however merit comment. First, and most importantly, the very small sample size, particularly in the ketamine study, preclude any strong inferences from these results, especially in relation to non-significant results. Thus, unfortunately, the current study is not properly powered to assess the outlined research questions and all reported results should be considered preliminary.

Second, we did not find any expected correlations at baseline between task measures and anhedonia symptomatology in patients at baseline. Again, the low sample size is likely to have obscured our ability to properly test this. Notably, however, the inclusion criteria for our patient cohort were based on a MADRS score of at least 20. Thus, the current study sample included participants at the extreme end of symptom severity, which likely restricted the symptom range. Future studies should explore this in cohorts with greater symptom variability and greater sample sizes. Similarly, the low sample size impeded any exploration of whether ketamine's effects on reward and punishment processes were associated with the anti-anhedonic or general anti-depressive effects.

A third limitation concerns the lack of computational models to examine performance on all the tasks. This limitation primarily pertains to the measure of exploration in the clock task. Although previous studies (Badre et al., 2012; Cavanagh et al., 2012; Frank et al., 2009; Kayser et al., 2015; Morris, Baek, et al., 2016; Strauss et al., 2011), have suggested that RT swings reflects goal-directed exploration, future studies need to employ a computational model to ascertain this assumption. This was not possible due to the lack of an existing model implemented in Stan for the clock task.

Fourth, four MDD patients were on current antidepressant medication during baseline testing, which may have affected the results. No sub-analysis was performed due to the limited interpretability with the low sample size. However, we note that a previous meta-analysis did not find that medication status exerted a significant influence on reward processing (Halahakoon et al., 2020).

Finally, due to the active status of the ketamine clinical trial at the time of writing, it was not possible to conduct official unblinding of treatment allocations. Ketamine and placebo randomisations were therefore guessed based on increases in blood pressure and CADSS scores post-infusions. However, it should be acknowledged that this resulted in effectively unblinding the trial, which ordinarily should not be done unless a medical emergency requires it. Unfortunately, this was necessary for completion of this thesis due to the extraordinary circumstances of Covid-19 which delayed the trial and prevented proper procedures in this instance. In addition, although the CADSS scores indicate that the current treatment allocation is correct, results should be interpreted with caution until unblinding can be performed.

5.5.6 Conclusion

In summary, across a battery of tasks measuring various aspects of reinforcement learning, decision-making and motivation, presumed ketamine increased exploratory behaviours and punishment learning rates in TRD patients, but did not significantly affect any other of the reward processes examined. No differences were detected between patients and healthy

individuals on any reward or punishment processing domain at baseline, although greater anhedonia severity was associated with greater (and potentially suboptimal) reward learning rates in patients. Taken together, these results indicate that ketamine might most prominently affect reward and punishment processing related to goal-directed behaviours. However, due to the preliminary nature of these results, future studies are required to replicate them and examine if other reward processing mechanisms not tested here might be more relevant to ketamine's anti-anhedonic effects.

6 General discussion

This chapter will synthesise the findings across experimental Chapters 2-5. Following brief overviews of each of the experimental chapters, highlighting the key findings, I will discuss how these findings provide insight into understanding anhedonia in relation to the models discussed in Chapter 1, and how they might relate to models of antidepressant action. I will then examine the potential implications and general limitations of the current work, and finally, general outstanding questions that could be addressed in future studies.

6.1 Chapter summaries

6.1.1 Chapter 2: Reliability of reward and punishment tasks

The test-retest reliability of eight reward and punishment tasks, spanning learning, valuation and decision-making, and motivated effort processes, was assessed in healthy individuals. The tasks were primarily chosen based on previous studies indicating that these processes might be important in anhedonia, depression, or other motivation-related psychiatric symptoms. Mixed reliability was found both across and within tasks. Both model-agnostic and computational measures of performance in the bandit task demonstrated fair-to-good reliability, while computational measures of performance in the gambling task outperformed (good-to-excellent) model-agnostic measures in the gambling task. Only uncertainty-driven exploration showed any reliability (good) in the clock task while the investor-trustee task had poor reliability. Finally, while the measured reliabilities of the physical effort measures were good-to-excellent, the cognitive effort tasks suffered from poor reliability in at least one task measure. Reliability was not assessed for the reward/punishment bias task due to a coding error that only came to light after the end of data collection. Overall, these results support the use of several tasks and their associated computational models, spanning different aspects of reward and punishment processing in a ketamine clinical trial.

6.1.2 Chapter 3: The spatiotemporal dynamics of motivation to exert cognitive effort: a simultaneous EEG-fMRI study

The goal of Chapter 3 was to explore and establish spatial and temporal neural markers of motivation to exert cognitive effort. This chapter reports the results of a simultaneous EEG-fMRI pilot study in healthy participants. At the time this approach was intended for future use in a ketamine clinical trial, although ultimately this was not implemented. The study used a novel calibrated cognitive effort task, categorising ten digits in a sequence as odd or even under time pressure, allowing the assessment of each participant's propensity to exert cognitive effort. This task addressed several shortcomings of existing cognitive effort paradigms. As expected, increasing effort decreased the probability to accept effort challenges, while increasing reward increased the probability of acceptance. Using fMRI, effort-related activation during the choice to accept was apparent in a number of PFC regions, including the ACC, dlPFC and vlPFC. In these regions an inverted U-shape of activation with increasing effort was observed consistently. The reasons underlying this pattern of activation are unclear, but future computational models may offer clarification. In the EEG analysis, a P3-like ERP peaking around 220-280ms had a greater amplitude for high than low effort. However, no corresponding regions were identified for this component in the fMRI analysis when using a trial-by-trial parametric approach incorporating the P3 amplitude. Thus, the relationship between temporal and spatial markers of effort sensitivity remains unclear. Although this study showed promise for examining spatial and, to some extent, temporal markers of motivation, for practical reasons it was unfortunately not possible to examine the effect of ketamine on the spatiotemporal dynamics of motivated cognitive effort.

6.1.3 Chapter 4: The effect of ketamine on fronto-striatal circuitry in depressed and healthy individuals: a resting-state fMRI study

The goal of Chapter 4 was to examine how ketamine affects fronto-striatal circuit connectivity in HCs and TRD patients. This was examined in a double-blind, randomised, placebo-controlled crossover trial in which individuals were examined two days post-infusions using rsfMRI. Ketamine modulated fronto-striatal circuitry in opposite directions in healthy and TRD

individuals: increasing functional connectivity between the striatum and PFC regions in TRD patients, while decreasing connectivity between these regions in healthy individuals, compared with placebo. Preliminary results did not provide strong evidence that these effects were driven by changes in peripheral inflammatory processes. However, associations between some of the fronto-striatal resting-state measures and improvements in anhedonia were observed, assessed both on the day of the scan and ten days afterwards. These results suggest that ketamine impacts a core brain circuit for motivational behaviours, which may underlie its effects on motivational symptoms and cognition.

6.1.4 Chapter 5: The effect of ketamine on reward and punishment processing in TRD

Chapter 5 examined whether ketamine affects cognitive and computational reward and punishment processing in TRD. In a randomised, double-blind, placebo-controlled, crossover study, TRD patients were tested on the four-armed bandit, reward/punishment bias, clock, and physical effort task from Chapter 2, one day post-ketamine and post-placebo infusions. Case-control comparisons before infusions were additionally conducted. No clear differences were found between TRD patients and healthy individuals on reward and punishment processes at baseline, although the relatively low number of participants affected statistical power. Similarly, presumed ketamine did not cause any significant changes in reward learning or sensitivity, reward or punishment response bias, motivation to exert physical effort, or go/no-go learning, although again statistical power may have limited the sensitivity of the analyses. However, and in line with predictions, presumed ketamine markedly increased exploratory behaviour, which here is tentatively assumed to reflect uncertainty-driven exploration (Frank et al., 2009); and to a lesser (although still substantial) effect punishment learning rates, although this is not in line with predictions. The results on exploratory behaviours provide preliminary support for the hypothesis that ketamine affects motivational symptoms in TRD through boosting reward-related processing, particularly suggesting that ketamine may modulate uncertainty-driven exploration, a cognitive process centrally implicated in goal-directed flexible behaviour. However, the small sample size limits any strong conclusions.

6.2 Ketamine's effects on motivational processes in relation to anhedonia models

6.2.1 Ketamine affects motivation-related neural circuitry previously implicated in MDD

In Chapter 4 we observed that ketamine increased functional connectivity between striatal and PFC regions in TRD patients. Under placebo, this circuitry showed lower functional integration, compared with healthy individuals. This is in line with a number of models of anhedonia that emphasise the importance of this circuitry in mediating reward-related symptoms observed in MDD and other disorders (Admon & Pizzagalli, 2015; Der-Avakian & Markou, 2012; Der-Avakian & Pizzagalli, 2018; Eshel & Roiser, 2010; Felger & Treadway, 2017; Husain & Roiser, 2018; Wang et al., 2021; Zhang et al., 2016). The present study thus adds to the growing literature suggesting disrupted fronto-striatal functioning in depression (Admon & Pizzagalli, 2015; Eshel & Roiser, 2010; Furman et al., 2011; Hamilton et al., 2018; Heller et al., 2009; Hoflich et al., 2019; Husain & Roiser, 2018; Kaiser et al., 2015; Pan et al., 2017; Price & Drevets, 2010, 2012; Sharma et al., 2017; Treadway & Pizzagalli, 2014; Wang et al., 2016; Yang et al., 2017).

Both human and animal findings have suggested that fronto-striatal interactions are crucial for motivated behaviour, through their role in integrating value signals with current goals to promote flexible responding (Balleine & O'Doherty, 2010; Haber, 2016; Haber & Knutson, 2010; Marquand et al., 2017). Dysfunction in these processes could manifest as various types of depressive symptoms and anhedonic profiles. Indeed, the prefrontal regions identified in the current study have been implicated in distinct aspects of goal-directed behaviour. While the dlPFC and vlPFC have been shown to modulate cognitive control and flexible behaviour, the OFC and pgACC have been linked more directly to reward learning and decision-making (Haber, 2016; Haber & Knutson, 2010; Insel et al., 2017). However, we see a notable difference from current models as a connection to the vmPFC was not evident in the current study. According to several studies in healthy individuals, rodents, and MDD/anhedonia models, the vmPFC might be important for reward valuation in concert with the striatum (Bartra et al., 2013; Felger & Treadway, 2017; Ferenczi et al., 2016; Morris, Kundu, et al., 2016; Pujara et al., 2016). It is not yet clear if this region is not as important in symptoms of anhedonia as previously thought, or if a task-based neuroimaging study might be more sensitive to probe striatal-vmPFC circuitry

(although previous studies, e.g., Felger et al. (2016) have identified such a circuit at rest), or if the parameters of the current study was not sensitive enough to identify this circuit (e.g., the timing of the fMRI scan might not have been ideal – discussed further in section 6.5.3 below). Consistent with a lack of change in striatal-vmPFC connectivity, we also did not observe that ketamine affected reward valuation in Chapter 5, although this null effect is difficult to interpret with the limited sample size in that study.

Nonetheless, these results provide the first clue that ketamine might affect motivation-related processes, implicating neural regions previously shown to be important for various goal-directed processes and which are known to be altered in MDD/anhedonia. Although resting-state fMRI studies can give us an idea of *which* neural regions might be affected by ketamine, and perhaps clues of which functions may be implicated, it is crucial to additionally understand *how* ketamine works by examining the cognitive computations. This is because to provide a complete explanation of ketamine's effects, ultimately, we are interested in behavioural outputs (Niv, 2021).

6.2.2 Presumed ketamine increases exploratory behaviours in TRD patients

To examine which cognitive mechanisms of motivational processes are impacted by ketamine, in Chapter 5 we homed in on specific processes related to learning, valuation, and motivated effort that have been shown to be relevant to motivation-related symptoms. Preliminary findings indicate that presumed ketamine predominantly influenced exploration, putatively by increasing uncertainty-driven exploration, and to a lesser extent punishment learning rates.

Adaptive learning and decision-making rely on a trade-off between immediate reward-maximisation (exploitation) and gathering information to find better reward values (exploration) (Gershman, 2019; Wilson et al., 2014). The trade-off between exploration and exploitation is a fundamental goal-directed function and a well-described problem in RL (Sutton & Barto, 2018). Yet, despite theoretical accounts emphasising an important role of goal-directed exploration in RL and in psychiatric disorders, very little is known about how it is

affected in MDD/anhedonia (Addicott et al., 2017; Huys et al., 2016; Scholl & Klein-Flugge, 2018). The current results provide preliminary evidence for the importance of goal-directed exploration in MDD, and aligns with a schizophrenia study showing lower uncertainty-driven exploration with greater anhedonia severity and general suboptimal explore-exploit decisions in MDD and schizophrenia (Blanco et al., 2013; Strauss et al., 2011). In RL, this might mean that ketamine affects the policy during learning (Gershman & Uchida, 2019). This could thus represent a possible cognitive process by which ketamine causes general changes in motivational states. Although we were unable to examine any associations with ketamine's anti-anhedonic effects due to the low sample size, and did not have a HC group to compare with, presumed ketamine's largest effects on the day of testing were on symptoms related to anticipatory anhedonia, dysfunctional attitudes, and self-efficacy. Speculatively, the increase in exploration might therefore be linked to these symptom changes although this needs to be tested in future studies. In line with this, a previous study indicated that individuals who more strongly believe that their choices can determine future events show greater uncertainty-driven exploration on the clock task (Kayser et al., 2015). However, again, future studies need to directly test this. It should also be noted that we did not find a correlation with anhedonia at baseline with performance on the clock task, nor a significant difference between MDD patients and HCs. It is too early to tell if this is due to a meaningful null effect, considering the low power in this study. It is also possible that the model-agnostic measure for exploration (overall RT swings) captures additional components not directly involved in uncertainty-driven exploration, making this measure a less sensitive index of exploration than a computational parameter (Frank et al., 2009).

In contrast to the dearth of research on goal-directed exploration in MDD/anhedonia, several studies have implicated depression and anhedonia-associated impairments in reward learning, reward valuation, and motivated effort (Halahakoon et al., 2020; Huys et al., 2021; Huys et al., 2013; Kieslich et al., 2022; Treadway & Zald, 2013). Among the most consistent patterns is a low sensitivity to rewards in anhedonia (Halahakoon et al., 2020), however we did not observe that presumed ketamine affected reward sensitivity across several tasks (the four-armed bandit, the

reward/punishment bias, and the physical effort task). In addition to the possible reasons discussed in Chapter 5, the reliability of reward sensitivity in the bandit task, as identified in Chapter 2, may not have been sufficient to examine this measure in a clinical trial. However, this would not necessarily explain the null effects on the other tasks, where e.g., reward sensitivity in the effort task showed excellent reliability (Chapter 2). One alternative interpretation is that these tasks address different facets of 'reward sensitivity'. Lack of converging validity across various tasks theoretically measuring the same concept has been identified for other processes, such as 'impulsivity' or 'risk preference' (Caswell et al., 2015; Pedroni et al., 2017). To disambiguate between these accounts, a greater sample size would be required.

Similarly, behavioural and neural-related motivated effort has been implicated across several motivation-related symptoms, which have motivated numerous models of anhedonia centred on impaired effort-related decision making processes (Culbreth et al., 2018a, 2018b; Husain & Roiser, 2018; Le Heron et al., 2018; Treadway & Zald, 2011, 2013; Zald & Treadway, 2017). In Chapter 3 we identified that the ACC was modulated by cognitive effort costs. Apathy in non-clinical samples has been associated with disrupted physical effort-related ACC function (Bonnelle et al., 2016; Hauser et al., 2017; Husain & Roiser, 2018; Le Heron et al., 2018). That the ACC was linked to cognitive effort-related computation here, might suggest that motivation-related symptoms are associated with domain-general effort-related ACC function. However, this hypothesis would need to be tested directly. In addition, physical effort-related ACC function has shown to be predictive of future vulnerability to psychiatric symptoms, suggesting a possible casual role of effort-related ACC function in mental illness (Armbruster-Genç et al., 2022). If alterations in effort-related ACC function represent a pathway to motivation-related symptoms, then these could represent a possible neural mechanism by which ketamine exerts some of its beneficial effects.

We did not however observe that presumed ketamine affected effort sensitivity or the overall probability to accept offers on the physical effort task version in Chapter 5. While unexpected,

it is difficult to draw conclusions based on null findings when the analysis only had power to detect very large effects. It is possible that ketamine's effects on effort-related processing might only be evident at a neural level, as some previous studies have only implicated altered effort-related ACC functioning, but no behavioural differences (Armbruster-Genç et al., 2022). It may also be that the behavioural effect is small and requires a larger sample size to detect or that it is absent. The neural circuit underlying effort-related computations in Chapter 3 was different to the circuitry found to be modulated by ketamine in Chapter 4. Although we identified the pgACC in Chapter 4, this region is quite distant from the more dorsally located ACC implicated in effort-related computations (Bonnelle et al., 2016; Hauser et al., 2017; Klein-Flügge et al., 2016). In any case, these effects are however not directly comparable since we were not able to examine the effect of ketamine on the neural mechanisms driving cognitive effort-based decision making.

An alternative explanation is that aberrant effort-related computations in MDD are associated with a specific anhedonic profile of increased inflammation, particularly in TRD (Felger & Treadway, 2017; Lucido et al., 2021). Preliminary evidence from Chapter 4 did not suggest that inflammation has a critical role in ketamine's beneficial effects. Although we did not examine inflammatory processes in Chapter 5, it is unlikely that we would have found a very different result to Chapter 4 in terms of inflammation since participants undergo a rigorous medical examination to rule out any possible unstable medical problems, which likely results in patients with low inflammation. This does not preclude the possibility that ketamine might still modulate these processes, but speculatively could point to subgroups of patients experiencing anhedonia. Of note, previous studies have implicated the ACC in ketamine's anti-anhedonic effects in TRD patients (Lally et al., 2014; Lally et al., 2015). These studies however examined resting-state glucose metabolism using PET two hours post-infusion, whereas the studies in Chapter 4 and 5 examined effects two and one days post-infusion, respectively. Thus, it is not clear if differences might be due to timing, insufficient power, or examination of different circuits (ACC effort versus striatal reward-driven networks). Examining rsfMRI might also differ from task-based fMRI. Unfortunately, it was not possible to examine the effect of ketamine on

the spatiotemporal dynamics of motivation to exert cognitive effort. Thus, it is yet not clear how ketamine might influence these neural computations, which should be elucidated in the future.

We also observed that depressed individuals with greater anhedonia had greater reward learning rates at baseline. Although we did not observe a significant relationship with the number of points won, the relationship between points won and reward learning rate was negative, possibly suggesting that high reward learning rates on this task are not adaptive. Speculatively, this might be related with mis-estimation of the volatility of the reward environment. For example, it is adaptive to have high learning rates (update more based on recent outcomes) when the environment is highly volatile (changes rapidly) but in less volatile environments, such as in the bandit task where the reward and punishment probabilities change slowly, a lower learning rate is more adaptive (Behrens et al., 2007; Pulcu & Browning, 2017). Whether this is due to a difference in RPE signalling, heightened sensitivity to omission of rewards, or suboptimal estimation of uncertainties (Pulcu & Browning, 2019) needs to be determined in future studies. Reward learning is however strongly associated with RPEs in the striatum (Nasser et al., 2017; Schultz, 2016), and although we observed that ketamine affected striatal functional connectivity in Chapter 4, unexpectedly no effect of presumed ketamine on reward learning was observed in Chapter 5. One possible reason is that the fronto-striatal changes are related to other goal-directed behaviours (discussed below) and the association between altered reward learning and anhedonia is subtle. Indeed, we did not observe any significant case-control baseline differences in reward learning despite large differences between groups on all motivation-related scales (Figure 5.7). Unfortunately, we were not powered to detect more subtle ketamine changes in Chapter 5. Consequently, this association with anhedonia is tentative and requires replication.

Finally, we also observed that presumed ketamine significantly increased punishment learning rates which was tentatively associated with more points lost, suggesting that this presumed ketamine-induced increase was maladaptive. This finding is surprising and difficult to interpret.

One possibility might be that it is related to the small (but non-significant) increase in state anxiety (Table 5.3) following presumed ketamine, since clinical anxiety has previously been associated with elevated punishment learning rates (Aylward et al., 2019). This could potentially suggest that ketamine does not provide beneficial effects across all reward and punishment aspects in TRD, in line with studies in healthy individuals showing that ketamine can impair aspects of RL (Vinckier et al., 2016). Importantly however, this effect was not *a priori* hypothesised and considering the very preliminary nature of this study, this effect is not interpreted further.

The current thesis was influenced by contemporary empirical and theoretical works of anhedonia implicating reward learning, value, and effort, as discussed in Chapter 1. However, these models are predominantly based on cross-sectional studies, limiting our understanding of the casual mechanisms related to anhedonia (Kieslich et al., 2022; Paulus et al., 2016). It has been argued that case-control studies may simply reiterate current psychiatric diagnoses, which do not necessarily advance our understanding of mechanisms underlying disorders (Redish & Joshua, 2016). Interventional studies are an alternative approach. Ketamine might offer a window into examining which aspects of reward processing are causally associated with anhedonia. In line with the theorised importance of fronto-striatal circuitry in anhedonia (Admon & Pizzagalli, 2015; Der-Avakian & Markou, 2012; Der-Avakian & Pizzagalli, 2018; Eshel & Roiser, 2010; Felger & Treadway, 2017; Husain & Roiser, 2018; Wang et al., 2021; Zhang et al., 2016), we observed in Chapter 4 that ketamine normalised this circuitry in TRD patients where functional connectivity between the caudate and vlPFC was associated with improvements in anhedonia. Likewise, one very tentative conclusion that might be drawn is that a cognitive mechanism underlying ketamine's antidepressant effects could be to ameliorate a lower tendency to explore actions.

6.2.3 How do the neural and cognitive effects of ketamine relate to each other?

The identified ketamine-induced changes in fronto-striatal circuitry in Chapter 4 have previously been associated with specific goal-directed behaviours. For example, lower VS-dlPFC functional

connectivity (identified under placebo in TRD participants versus HCs) has been associated with impaired cognitive flexibility, while lower connectivity between the VS (including the VRP) and lateral OFC has been associated with slower updating of value representations to guide optimal decision-making during a reversal learning task (Clark et al., 2004; Morris, Kundu, et al., 2016). These findings suggest that ketamine's fronto-striatal effects may be related to flexible use of reward-related information to optimise behaviour. It is not clear whether these fronto-striatal shifts are related to the presumed ketamine-induced increase in exploratory behaviours in Chapter 5, as no behavioural data were collected in Chapter 4; however optimally balancing exploration against exploitation requires similar flexible behaviours. Uncertainty-driven exploration in this task and others has also consistently been associated with PFC, specifically rlPFC, function (Badre et al., 2012; Cavanagh et al., 2012; Frank et al., 2009; Morris, Baek, et al., 2016; Tomov et al., 2020; Zajkowski et al., 2017), and others have also emphasised the OFC (Costa & Averbeck, 2020). It has further been suggested that the striatum is also involved in exploratory decisions (Costa et al., 2019), although others emphasise an exploitation, rather than exploration, role of the striatum (Frank et al., 2009; Maia, 2009). The rlPFC was however not identified in the fronto-striatal circuitry in Chapter 4. How exactly the striatum and PFC interact during explore-exploit decisions remain to be determined (Hogeveen et al., 2021) but may be broadly consistent with the results from Chapter 4.

A potential unifying account involves the dopaminergic system. Striatal and PFC functioning, and uncertainty-driven exploration have consistently suggested an important role of dopamine. For example, Frank et al. (2009) identified that a gene controlling PFC dopamine function was specifically associated with uncertainty-driven exploration on the clock task (but see Gershman and Tzovaras (2018)), while genes involved in striatal dopamine functioning were involved in exploitative decisions, suggesting dissociative roles of dopaminergic functions in the PFC and striatum to explore-exploit trade-off decisions. This is in line with other studies indicating that greater prefrontal dopaminergic tone is associated with goal-directed exploration (Blanco et al., 2015; Kayser et al., 2015). Decreased functional connectivity between the striatum and PFC has also been found following dopamine depletion, which was further associated with reduced

performance during a set-shifting task (Nagano-Saito et al., 2008). Several studies indicate that ketamine has downstream dopaminergic effects (Belujon & Grace, 2014; Collo & Merlo Pich, 2018; Kokkinou et al., 2018; Rincón-Cortés & Grace, 2020) and can strengthen weakened VTA-PFC connectivity in a rodent helplessness model through glutamatergic and dopaminergic signalling, ameliorating depressive-like behaviours (Wu et al., 2021). Notably, uncertainty-driven exploration is associated with increased functional connectivity between the striatum and PFC, particularly the lateral frontopolar cortex (Morris, Baek, et al., 2016). Tentatively, the findings in Chapter 4 and 5 are associated with glutamatergic and dopaminergic signalling in the fronto-striatal circuitry. However, this needs to be tested directly. Furthermore, it is not clear whether these effects might be specific to the striatum, PFC or signalling between these regions, or whether other neurotransmitters, such as acetylcholine and norepinephrine (Addicott et al., 2017; Yu & Dayan, 2005), might also play an important role.

6.3 How do these findings relate to models of antidepressant action?

6.3.1 Neuroplasticity models

Neuroplasticity models of antidepressant action emphasise that dysregulation of homeostatic neural mechanisms might lead to altered functional connectivity in depression, particularly within cortico-limbic-striatal circuitry (Duman & Aghajanian, 2012; Price & Drevets, 2010). Ketamine may subsequently partly act by restoring disrupted homeostatic regulation (Duman & Aghajanian, 2012; Duman et al., 2019; Nugent et al., 2019). The current thesis has not specifically tested any models of neuroplasticity directly, however some of the findings might be consistent with such a model.

Specifically, the results from Chapter 4 may partially support such an account, at least at the neural circuit level, given that increased anti-anhedonic effects were associated with greater functional connectivity post-ketamine between the caudate and vlPFC. If ketamine affects homeostatic neural regulation in general, this may also explain why ketamine may restore neural regulation in individuals with depression but disrupt fronto-striatal functioning in healthy individuals. The initial functioning of the fronto-striatal circuitry might therefore be

important in determining the response to ketamine. However, a more direct test of this hypothesis would be to examine baseline fronto-striatal circuitry.

It remains unclear whether presumed ketamine's effects on exploration can be attributed to restoration of homeostatic mechanisms. We were restricted by sample size to examine any associations with ketamine's anti-anhedonic effects, and did not have a HC group to compare with, nor did we directly examine any neural processes. Interestingly, some accounts of the explore-exploit trade-off are consistent with the notion that it follows homeostatic principles (Addicott et al., 2017). Adaptive goal-directed behaviour relies on striking a balance between exploring and exploiting options, which may follow an inverted U-shaped pattern (Addicott et al., 2017). Thus, maladaptive decisions might be driven by extreme biases at either end of the explore-exploit trade-off when these strategies are not adaptive to the environment: too much exploitation/too little exploration or too much exploration/too little exploitation. In this model, it has been suggested that motivational impairments might be related to low exploration/overly exploitative decisions (Addicott et al., 2017). PFC dopaminergic modulation of cognitive functions may also follow an inverted U-shape where optimal functioning lies in the middle (Cools & D'Esposito, 2011; Weber et al., 2022). Speculatively, these results might reflect the downstream effects of ketamine on a relative shift in dopaminergic modulated striatal-PFC balance.

Considering the complexity of the dopaminergic system and interaction with ketamine, the above explanation is likely an oversimplification. It is also not clear how such an explanation might fit with the differential effects of ketamine on fronto-striatal circuitry in patients and HCs, unless low functional connectivity can be the result of both 'too little' and 'too much' (i.e., suboptimal) dopamine levels, which has been suggested previously for other cognitive functions (Wallace et al., 2011). In addition, it is unclear how ketamine would affect exploration in HCs, as according to this account it would make them even more exploratory, which is still maladaptive; however, it is less clear how increased exploration would then be associated with motivational-related symptoms in TRD, unless it perhaps involves random exploration as

previously observed in anhedonia (Robinson & Chase, 2017). This would require additionally examining the interplay between random and directed exploration. Future studies will need to address these questions and directly examine whether the current findings stem from altered glutamate and dopaminergic synaptic plasticity in reward-circuitry and interact with baseline dopamine levels.

6.3.2 Cognitive neuropsychological model

There is a lack of cognitive models of ketamine's antidepressant mechanisms, owing to the dearth of studies examining ketamine's cognitive mechanisms. The cognitive neuropsychological model suggests that ketamine directly affects 'top-down', putatively PFC-associated, negative priors (Roiser et al., 2012). This type of negative schema might rely on previously acquired negative memory-associations that ketamine abolishes (Godlewska & Harmer, 2021; Harmer et al., 2017; Stuart et al., 2015). However, we did not examine memory-related functions here or negative schemata. In addition, it is not entirely clear how these mechanisms relate to negative mood versus anhedonia. As discussed in Chapter 5, ketamine has previously shown to influence a 'higher-level' confidence parameter that modulated exploration (Vinckier et al., 2016), suggesting that ketamine affects the precision of beliefs about the world, in relation to reward statistics. Such an account could fit with the cognitive neuropsychological model that suggests that ketamine affects priors, but was not directly tested here. In addition, this model does not adequately address the different effects of ketamine in patients and HCs, as observed in Chapter 4.

Interestingly, a recent model of ketamine's psychomimetic effects in healthy individuals and antidepressant effects in MDD, the 'continuum hypothesis of psychotomimetic rapid antidepressants', proposes that ketamine might increase cognitive flexibility by decreasing the precision of overly precise prior expectations ('inflexible thinking') in depression (Haarsma et al., 2021). This is based on a Bayesian account such that the prior is represented by a distribution with a mean and variance, and the proposal suggests that ketamine increases the variance of this distribution. Here, cognitive inflexibility is thought to relate to depression by

constraining beliefs about affective events, such that the probability of negative events is overweighted, and positive events underweighted. Putatively, the latter would be associated with anhedonia. Interestingly, NMDA receptors are thought to code the precision of prior beliefs (based on a Bayesian predictive coding account) (Corlett et al., 2016) and ketamine-induced negative symptoms have previously shown to be positively correlated with PFC NMDA receptor binding (Stone et al., 2008). Speculatively, our results could align with such an account since exploration is broadly related to behavioural flexibility. As noted, lower VS-dlPFC functional connectivity has previously been associated with impaired cognitive flexibility (Morris, Kundu, et al., 2016), which was normalised by ketamine in Chapter 4. Goal-directed behaviour also relies on behavioural flexibility to adaptively balance exploration with exploitation (Addicott et al., 2017). However, whether this model can account for the results in Chapter 4 and 5 and the opposing symptom and neural effects of ketamine in healthy versus depressed individuals remains an open question.

6.4 Implications of the research

6.4.1 Chapter 2

Chapter 2 has several implications, particularly for translating cognitive neuroscience to clinical trials. Reliability in cognitive neuroscience has garnered increased attention in recent years, with worryingly low reliability across conventional measures from both cognitive tasks and functional neuroimaging (Elliott et al., 2020; Enkavi et al., 2019; Frey et al., 2017; Noble et al., 2019; Nord et al., 2017; Rodebaugh et al., 2016). While questionnaires are usually systematically examined for validity and reliability before use, this criterion is rarely applied for cognitive tasks (Horan et al., 2015). This is partly due to cognitive tasks being considered more objective and directly relevant to examining mechanisms underlying behaviour and therefore changes to treatment (Goldberg et al., 2010). In Chapter 2, although most tasks had at least one measure with some degree of reliability, this study shows that reliability of cognitive measures cannot be assumed. Reliability is thus a crucial, but often neglected, consideration for any successful attempts at applying a cognitive neuroscience approach to psychiatry. In particular, it is important to have sufficient reliability for within-subjects study designs, such as a crossover

randomised control trial, and longitudinal designs. Poor reliability in these contexts will add noise to measures of interest and decrease the sensitivity to detect effects of interest. Illustrating this point, only the measures from Chapter 2 that showed at least a good level of reliability showed an effect of ketamine in Chapter 5 (RT swings and punishment learning rate).

It is however unlikely that computational modelling is a panacea to this problem. The model-agnostic measures on the bandit task exhibited similar reliability to the computational measures. Model-agnostic measures of cognitive tasks have often been reported to exhibit poor-to-moderate reliability (Enkavi et al., 2019; Hedge et al., 2018; Rodebaugh et al., 2016). It has been argued that this may be due to their inability to capture the generative process underlying task performance (Huys et al., 2021; Price et al., 2019). However, our results suggest that it should not be assumed that computational parameters will always provide greater reliability than non-computational ones. That said, the model-agnostic outcome measures represent more distal proxies of the processes driving behaviour on the bandit task, as it is difficult to compute model-agnostic equivalents of some parameters, such as reward/punishment sensitivity. Importantly, computational models make explicit and falsifiable predictions about the components driving behaviour, which can be refined and used to simulate artificial data to generate new predictions. Thus, computational modelling is a more rigorous and preferable method for assessing behaviour than model-agnostic measures, which, unlike computational methods, lack the mechanistic insights into the underlying processes generating behaviour.

Contemporary approaches to psychiatry, such as RDoC, emphasise dimensional, instead of categorical, frameworks (Insel et al., 2010). This is based on the premise that psychiatric disorders do not have discrete underlying explainable cognitive and neural mechanisms but might be better represented along various dimensions. That is, individual differences rather than group differences should be the focus. Moreover, group effects are invariably not predictive of individual scores, as different statistics are used for these different purposes (e.g., correlation versus t-test) (Fisher et al., 2018; Fröhner et al., 2019; Hedge et al., 2018). Thus,

reliability is also an important consideration for studies assessing individual differences (Fisher et al., 2018). The current results highlight this, as the majority of the reliable measures (e.g., punishment learning rate, physical effort sensitivity, and exploration) have also previously been associated with individual differences in prior studies (Aylward et al., 2019; Bonnelle et al., 2016; Strauss et al., 2011), as they were in the current study (Chapter 5: reward learning and anhedonia).

6.4.2 Chapter 3

The results from Chapter 3 have several implications. Firstly, this study indicated that our novel task, which was designed to overcome several limitations of currently used cognitive effort tasks and provide a patient-friendly paradigm, appears to be appropriate for probing motivation to exert cognitive effort. Although cognitive effort is a ubiquitous function, allowing us to adjust how much we engage with cognitively demanding tasks, it has received very little attention in research on anhedonia. It may also be an important mediator of various other cognitive functions, such as cognitive fatigue, habitual versus goal-directed behaviour, logical reasoning, and cognitive control (Boksem & Tops, 2008; Müller & Apps, 2019; Otto et al., 2015; Westbrook & Braver, 2015). In addition, cognitive effort is associated with real-life outcomes such as academic achievement (Shenhav et al., 2017). The current task design was based on a physical effort paradigm, previously mainly used in research on apathy. The current study provides an important extension of this work, meaning that decision making relating to both physical and cognitive effort can be probed to examine if any impairments identified are domain general or specific.

Secondly, even though EEG provides a more direct readout of the neuronal activity underlying cognition than fMRI, EEG research on effort-based decision making is scarce. In combination with fMRI, the neural processes driving decisions may be more precisely characterised (Pisauro et al., 2017). We identified a P3-like ERP that was related to cognitive effort level during decisions to accept an offer. The P3 ERP has previously been associated with motivational symptoms. For example, lower P3 amplitude during focused attention was associated with

greater symptoms of anhedonia, while a negative association between the P3 and symptoms of apathy was observed in an MID-like task (Dubal et al., 2000; Takayoshi et al., 2018). Similarly, effort-related ACC responses have been associated with apathy (Bonnelle et al., 2016; Hauser et al., 2017). Thus, the current study identified two neural signals known to be important in motivation-related symptoms. However, this will need to be assessed directly in future studies. Whether these two neural signals are related or represent different effort evaluation processes remains undetermined, since we were unable to identify a neural generator of this P3 in the current study.

6.4.3 Chapter 4

The results of Chapter 4 indicate that fronto-striatal functional connectivity might be an important mechanism underlying ketamine's beneficial effects. Increased fronto-striatal connectivity post-ketamine was associated with sustained improvements (ten days post-infusion) in anhedonia, but not general depressive symptoms, in TRD participants. The effects were most prominent for striatal interactions with the pgACC, although all PFC regions showed similar patterns. Changes in this circuitry might therefore drive ketamine's sustained motivational symptom improvements. It is however not entirely clear if there are different neural mechanisms associated with different stages of ketamine's anti-anhedonic effects. These results should also be considered preliminary due to the small sample size. If replicated, this ketamine-induced change in fronto-striatal circuitry could potentially serve as a predictor of sustained ketamine response, as suggested for other early cognitive and neural signs of antidepressant response (Browning et al., 2019). Speculatively, in such a case, it might represent circuitry to target in order to prolong the beneficial effects of ketamine, or use as a neural marker when screening anti-anhedonic responses of novel drugs during development (Krystal et al., 2020).

A strength of this chapter was the inclusion of healthy individuals to compare ketamine effects with. Usually, ketamine trials in TRD patients only include healthy individuals pre-treatment or not at all. In other approaches, the mechanisms of ketamine's antidepressant effects have been

examined using healthy individuals only. Indeed, it has been suggested that HCs may be useful for understanding mechanism of action of antidepressant drugs (Pringle et al., 2011). However, in the current study, ketamine showed opposite effects on the fronto-striatal circuitry than TRD patients, suggesting that it might not be appropriate to extrapolate ketamine's mechanism of action based on results from a non-depressed sample.

In addition, these results suggest that perhaps instead, ketamine's effects in healthy individuals could potentially be used as a model of anhedonia (Nugent et al., 2019). This would be similar to how ketamine's psychomimetic effects in HCs have been used to test mechanisms underlying psychosis in schizophrenia (Corlett et al., 2016; Frohlich & Van Horn, 2014). Ketamine has also been used to examine negative symptoms of schizophrenia, albeit to a far lesser extent than positive symptoms of schizophrenia (Driesen et al., 2013; Pollak et al., 2015; Stone et al., 2008; Thiebes et al., 2017). To validate this approach, ketamine in healthy individuals could be used to examine which aspects of anhedonia in MDD can be mimicked and further test theories of ketamine's mechanism of action, such as the 'continuum hypothesis of psychotomimetic rapid antidepressants' (Haarsma et al., 2021). To extend this further, such an approach could potentially compare ketamine-induced anhedonia with other approaches, such as inflammation induction (Lucido et al., 2021), to generate new hypotheses of mechanisms underlying anhedonia.

Using ketamine in healthy individuals as a model of anhedonia has been suggested previously using the same sample as in Chapter 4. This was based on the observation that ketamine acutely, transiently, and mildly increases motivation-related symptoms in HCs (Nugent et al., 2019). Notably, in this study, every item on the SHAPS, but those relating to appetite, increased in HCs but decreased in patients. We extend this proposition by showing that ketamine impacts a neural circuit important for motivational behaviours in both populations.

6.4.4 Chapter 5

An unexpected finding in Chapter 5 was that greater anhedonia was associated with *higher* reward learning rates. This finding contrasts with previous studies suggesting that MDD and depression is associated *lower* reward learning rates (Brown et al., 2021; Chase et al., 2010). However, recent studies highlight that RL parameters measured in one task may not generalise to another, especially learning rates (Eckstein, Master, et al., 2021; Eckstein, Wilbrecht, et al., 2021). This has a broader implication for fields such as computational psychiatry. For example, it implies that associations between symptoms and RL parameters need to be carefully evaluated in relation to the context in which they are studied, and concluding that (for example) low reward learning rate in general is associated with anhedonia might not be valid. Despite this, no similar associations were found in the model-agnostic measures, highlighting the utility and sensitivity of computational methods to understand behaviour here, if replicated.

6.5 Limitations

6.5.1 Statistical power

A major limitation across multiple chapters, particularly Chapters 3, 4 and 5 concerns the sample size. In Chapter 3 this might have primarily interfered with our ability to properly characterise the time course of decisions involving effort execution since EEG data tend to suffer from poor signal-to-noise at the single trial level (Luck, 2014). To counterbalance this, an increase in trials or participants would be needed.

Importantly, this limitation strongly constrains conclusions in Chapter 4 and 5, which were the main studies assessing ketamine's effects on motivational processes. For example, in Chapter 4 and 5, we were 80% powered to detect only very large effect sizes (Chapter 4: d=0.9, Chapter 5: d_z=1.07). This means that smaller, but potentially interesting effects, will very likely have been missed. The small sample size in both of these studies was mainly due to challenges associated with a rigorous study design and recruiting a specific patient population. Importantly, null effects are difficult to interpret considering low power. For example, the effect sizes we were

powered to detect are higher than the previously reported anti-anhedonic effects of ketamine (around *d*=0.8 one day post-infusion) (Lally et al., 2014). Similarly, we were likely underpowered to detect any differences between patients and healthy individuals on cognitive measures considering that previous studies suggest that effect sizes for case-control differences in reward processing range from small to medium for RL impairments (*d*=0.35) and medium to large for reward bias (*d*=0.64). By comparison, we had 80% to detect an effect size of around *d*=1 when examining case-control differences in effect size in Chapter 5, which is substantially larger than previously observed differences in reward processing between healthy individuals and patients (Halahakoon et al., 2020). This may also explain why we did not replicate the expected significant improvements in symptoms following presumed ketamine, as previously reported across various studies and cohorts (Coyle & Laws, 2015; Fond et al., 2014; Kishimoto et al., 2016; McGirr et al., 2015; Wilkinson et al., 2018). These issues may have thus impeded our ability to properly characterize ketamine's effects on fronto-striatal connectivity, and particularly its effects on reward processing. In addition, this limitation obscured our ability to investigate any associations between presumed ketamine-induced changes in reward and punishment tasks and changes in motivational symptoms in Chapter 5. In light of this limitation, findings presented in this thesis are tentative and require replication using larger sample sizes.

6.5.2 Blinding in ketamine studies

A common criticism of saline placebo-controlled, double-blind trials of ketamine is that these are not truly blinded, since the side effects of ketamine may immediately unblind participants (Murrough et al., 2013). Although this is a valid concern, importantly, studies employing an active control, such as midazolam, still show a significant antidepressant response in TRD patients (Murrough et al., 2013; Shiroma et al., 2020). In addition, the strength of ketamine's side effects and its beneficial effects are not straight forward. For example, increasing the ketamine dosage, which increases the dissociative effects, does not seem to increase the antidepressant effects of ketamine (Fava et al., 2020), and in general the evidence that dissociation is necessary for ketamine's antidepressant response is weak (Ballard & Zarate, 2020). Furthermore, the current focus of this thesis was not to assess ketamine's efficacy,

which has been established previously (Coyle & Laws, 2015; Fond et al., 2014; Kishimoto et al., 2016; Kryst et al., 2020; McGirr et al., 2015; Wilkinson et al., 2018). Instead, the focus of our experiments was to understand the mechanisms of action of ketamine. Introducing an active placebo agent such as midazolam might therefore have rendered our results difficult to interpret.

6.5.3 Testing time-window

Another potential limitation concerns the time-window used to assess ketamine-associated effects on motivational processes. Ketamine produces rapid-acting improvements in anhedonia. For example, in Chapter 4, these effects were evident from 40 minutes post-infusion. However, the rsfMRI scan occurred two days post-infusion. Similarly, we administered the reward and punishment processing tasks one day post-infusion. A complication of investigating mechanisms of rapid-acting antidepressants is that it is difficult to establish mechanisms prior to the emergence of symptom changes (Kotoula et al., 2022). It is, for example, possible that ketamine produces immediate changes in cognitive and neural motivational processes that drive its anti-anhedonic effects, which might be different from the more sustained anti-anhedonic response. For example, a recent study in rodents indicated separate PFC mechanisms driving ketamine's acute (within hours) antidepressant-like effects than its more sustained antidepressant-like effects (12-24h post-ketamine) (Moda-Sava et al., 2019). Whether such time-dependent differences in mechanisms can be observed in TRD patients remains to be tested. However, we chose to test reward processing one day post-infusion in Chapter 5 as ketamine's anti-anhedonic effects have previously shown to peak at this time (Lally et al., 2014; Zarate et al., 2006). This therefore allowed us to increase our sensitivity to detect ketamine-induced effects on motivational processes. The effect size of ketamine's anti-anhedonic effects was also medium-to-high in Chapter 5, and were also robust at the scanning timepoint in Chapter 4. Importantly, these timepoints were chosen so that ketamine would be fully metabolized at the time of testing, meaning that the results would not be confounded by ketamine's direct pharmacological effects. Nevertheless, it is likely that there are individual differences in the trajectory of ketamine's beneficial effects, and it will be

important for future studies to map ketamine's cognitive and neural reward effects across different timepoints and examine their relationship to different symptom dimensions.

6.6 Future directions

6.6.1 Leveraging multiple measures to pinpoint ketamine's beneficial effects

Although we argue that neural and cognitive measures offer more precise and mechanistic insight into ketamine's beneficial effects, self-report scales are currently the main tool to assess treatment effectiveness and must therefore be part of clinical endpoints. An outstanding question is how changes in symptoms, cognition and neural function following ketamine are related. One problem with simply correlating several measures with each other is that it may miss important effects. As an example, exploration has shown to be higher in individuals with high anxiety (Aberg et al., 2021) but has also been observed to be lower in anhedonia (Strauss et al., 2011). Appropriately teasing these accounts apart is challenging, especially when studies are based on symptom-clusters such as in case-control designs. One way to extend simple correlations between multiple measures is to examine shared features among measures through data reduction techniques such as factor analysis (e.g., (Gillan et al., 2016; Rouault et al., 2018)). This has been shown to be valuable for uncovering the symptom dimensions associated with metacognition (Rouault et al., 2018), goal-directed control (Gillan et al., 2016), and tentatively, ketamine response (Ballard et al., 2018), which was not apparent with standard scales. In Chapter 5, a broad set of symptom scales was administered, including several measures of motivation-related symptoms. However, due to the small sample size, performing a factor analysis was not possible. Future studies may benefit from this approach in larger sample sizes. This can also be extended into identifying overlapping and distinct reward and punishment constructs using task measures, and for example, address the question of whether reward sensitivity across tasks taps into the same concept.

6.6.2 Predicting the anti-anhedonic response to ketamine

The current work has focused on understanding the mechanisms of action of ketamine; that is, which processes *mediate* ketamine's beneficial effects. However, it will also be important to

establish the mechanisms predicting (moderating) response to ketamine. This has the potential to establish biomarkers and identify for whom treatments might work and thus optimize treatment selection (Kraemer et al., 2002). This is a key objective of many goals of psychiatry (Browning et al., 2020; Paulus et al., 2016), but as of yet has remained elusive. Moderation can be studied by assessing pre-randomisation measures of cognitive, neural and computational processes and examining how these may predict response to a treatment (but not a control intervention) in the context of a randomised clinical trial (Kraemer et al., 2002). To qualify as a prognostic marker, the measure must be reliable. From Chapter 2, potential cognitive markers may thus include the RT swing measure in the clock task, reward and punishment learning in the bandit task, and all measures from the physical effort and gambling tasks. To take a step further, such mechanistic measures could potentially be combined and used to predict response using machine learning techniques, although it should be noted that this approach requires large samples. If based on theoretically-relevant features, this approach may prove useful in predicting treatment response (Huys et al., 2016; Paulus et al., 2016). For example, multivariate task measures have shown to predict response to SSRIs in a large study (Etkin et al., 2015).

6.6.3 Other putatively important cognitive processes in anhedonia

This thesis has focused on processes relating to various aspects of reward and punishment, reflecting the current state of knowledge of cognitive mechanisms underlying anhedonia in MDD, almost entirely derived from cross-sectional studies (Halahakoon et al., 2020; Kieslich et al., 2022). However, the mechanisms underlying anhedonia are not well understood, and as discussed earlier, a more promising approach to this question will be to causally examine mechanisms in interventional studies, as well as in longitudinal studies. Other processes than the ones examined in this thesis might be important for ketamine's anti-anhedonic effects. For example, it has recently been proposed that current paradigms examining mechanisms of anhedonia may be insufficient in capturing the nature of impairment, as these are typically unidimensional in design (e.g., assume a single value function) (Huys & Browning, 2021). A limitation of the unidimensional approach is that it does not allow for examining how valuation

depends on internal states of agents. The idea here is that it matters less how "good" an outcome is in driving behaviour, but more how well aligned rewards are with the agent's goals. This type of framework draws on classical drive-reduction theories of motivation which are based on homeostatic principles (Juechems & Summerfield, 2019; O'Reilly, 2020). Future studies may therefore benefit from incorporating more complex task designs (i.e., multidimensional value/goals) in which this can be examined.

To further understand ketamine's effects on exploration, paradigms based on foraging theory might be of interest. These tasks are not based on choosing between two options but instead whether to engage with a current option or decide to opt-out of a default state to explore for other opportunities (Scholl & Klein-Flugge, 2018). This framework might provide a more ecologically valid setting, since most real-world decisions are of this type – such as the example given at the start of this thesis of getting up from the sofa (default) to find a cookie in the kitchen (foraging); for this reason, foraging is often used to study decision making in animals (Addicott et al., 2017). Interestingly, these kinds of decisions have been shown to rely on the ACC, which has been proposed to signal the value of exploration (Kolling et al., 2016).

6.7 Conclusion

Our lack of understanding of treatment mechanisms contributes to the trial-and-error approach in treatment selection in psychiatry and difficulties in developing more efficient treatments. The primary aim of the current thesis was to better understand how ketamine, a relatively novel rapid-acting antidepressant, exerts its effects. Tools from cognitive neuroscience were used to address this question, which have previously been underutilised in understanding how ketamine works. Specifically, I examined candidate neural, cognitive, and computational mechanisms of motivational processes, since ketamine has previously shown to affect motivation-related symptoms (Lally et al., 2014; Lally et al., 2015; Nugent et al., 2019). This thesis tentatively suggests that ketamine most prominently enhances functional connectivity between the striatum and PFC in TRD, neural circuitry known to underlie reward-related processing. We also found that ketamine increased exploratory behaviour in TRD patients,

putatively related to goal-directed uncertainty-driven exploration. However, we failed to find evidence of ketamine-associated improvements in other reward-related mechanisms previously strongly associated with anhedonia, such as reward sensitivity, reward learning, and effort-based motivation. While this could suggest that these cognitive mechanisms are not as strongly related to ketamine's beneficial effects, this thesis is unable to draw that conclusion due to the small sample size in Chapter 5.

Speculatively, these findings might reflect to downstream plasticity effects of ketamine on dopaminergic systems, a prediction that needs to be tested in future work. Whether current neural and cognitive theories of antidepressant action are sufficient to account for these findings is not clear. The ketamine-induced neural shifts could potentially be consistent with neuroplasticity models of ketamine's antidepressant effects in terms of regulating neural homeostatic balance. However, a more complete model will need to link across cellular and cognitive levels and attempt to incorporate findings of differential effects of ketamine in patients versus healthy individuals, as observed in Chapter 4. Such an attempt has not been made here, but it has been highlighted that current theories of antidepressant action cannot adequately explain all these findings.

In contrast to traditional antidepressants, ketamine rapidly improves symptoms, and specifically anhedonia. Understanding its mechanisms therefore offers potential in advancing our understanding of both more targeted and more efficient treatments of anhedonia, as well as the aberrant mechanisms maintaining anhedonia. This thesis has provided very preliminary evidence of potential neural and cognitive mechanisms with the hope that this will inspire future work that one day might advance the treatment of depression.

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