Anhedonia in Depression: The Effects of Conventional Antidepressants and Ketamine on Reward Processing

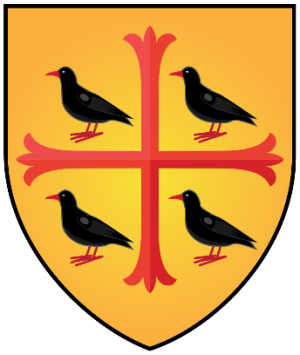
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Thesis submitted for the degree of DPhil Psychiatry

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Declaration of Authorship

I, Chloe Wigg, confirm that the work presented in this thesis is my own. Where information has been drawn from other sources, this has been properly acknowledged.

Abstract

Reward processing involves anticipating rewards and losses, learning from them, experiencing pleasure, and guiding behaviour. These processes are disrupted in depression, particularly in relation to anhedonia, a core feature of depression. However, it remains unclear which components are most affected and how they are modulated by antidepressant treatments. Conventional antidepressants have limited effects on anhedonia. Ketamine produces rapid antidepressant effects and may have anti-anhedonic properties, although its underlying mechanisms remain unclear.

This DPhil thesis investigated reward and loss processing in depression using a probabilistic instrumental learning task with monetary wins and losses and an effort-based decision-making task assessing willingness to exert effort for different reward amounts.

Study 1 used an online observational sample (N=1,917) to examine associations between depressive symptoms, antidepressant use, and reinforcement learning. Greater depressive symptom severity was associated with reduced learning from loss, reflected in lower loss learning rates, with no effects in the reward condition. In individuals with Major Depressive Disorder taking conventional antidepressants (N=124), antidepressant use was associated with higher loss learning rates, reduced choice stability, and poorer optimal choice accuracy on loss trials, with no effects in the reward condition.

Study 2 investigated the effects of ketamine in treatment-resistant depression (N=60) using a placebo-controlled, double-blind design with fMRI, questionnaires, and behavioural tasks. At 24 hours post-infusion, ketamine altered neural responses to win and loss outcomes (monetary feedback) across cortico-striato-limbic circuitry and increased insula responses to loss-related

prediction errors, without behavioural changes. Thirty minutes post-infusion, the ketamine group showed a greater decrease in reaction time as reward increased, and changes in reward valuation in offer acceptance were observed at seven days. Depressive symptoms improved over one week, whereas anhedonia and other reward measures did not significantly change. Overall, this thesis applied a reward processing framework to understand mechanisms underlying depression and its treatment.

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Chapter 1: Introduction

1.1 Major Depressive Disorder: Burden, Impairment, and Unmet Need

Major Depressive Disorder (MDD) is among the most common and disabling psychiatric disorders worldwide (GBD 2019 Mental Disorders Collaborators et al., 2022). For many individuals, depression significantly alters how everyday life is experienced and navigated. Activities that were once routine can become effortful or unmanageable. Social relationships may feel distant or difficult to sustain, and motivation, interest, and desire for connection are often diminished, with engagement in work or education frequently disrupted. These difficulties are not transient challenges but persistent functional impairments that affect independence, identity, and quality of life. These functional consequences also influence how and when individuals are able to seek and engage with treatment. When motivation is reduced, decision-making is slowed, and effort itself is experienced as costly, initiating and sustaining treatment engagement can be particularly challenging. Although a range of psychological and pharmacological treatments are available and can be effective (Cipriani et al., 2018), a significant proportion of individuals experience only partial response, residual symptoms, or recurrent relapse (Kessler & Bromet, 2013; Rush et al., 2006). As a result, many people continue to live with clinically significant symptoms that interfere with daily functioning even while receiving treatment. Despite substantial advances in available treatments, depression remains difficult to treat effectively for many individuals, highlighting the need for a more precise understanding of mechanisms that contribute to persistent symptoms and functional impairments.

1.2 Heterogeneity and the Limits of Diagnostic Categories

Over several decades of research, it has become increasingly evident that Major Depressive Disorder has a wide range of clinical presentations. More than 16,400 distinct symptom combinations meet formal diagnostic criteria for MDD (Fried & Nesse, 2015), meaning that

individuals who share the same diagnosis may differ significantly in the processes most relevant to their impairment. For some individuals, persistent low mood may be the most impairing, whereas for others, reduced motivation, blunted responsiveness to rewarding or positive events, or heightened sensitivity to negative outcomes may drive impairment across one or more domains. This heterogeneity presents a major challenge for both research and clinical practice. In treatment, it limits the precision of treatment selection and outcome prediction, and response can vary widely even among individuals with similar overall symptom severity. More broadly, current diagnostic classification systems define depressive disorders in terms of symptom clusters rather than underlying aetiology or pathophysiology (Hyman, 2007). While this symptom-based approach is useful in clinical practice and for diagnostic assessment, there is an urgent need to better understand the neurobiological and cognitive mechanisms underlying the symptoms and explain individual differences in impairment and treatment response.

These challenges have motivated a shift toward approaches that move beyond categorical diagnoses and focus instead on neurocognitive domains. Such domains, including motivation and reward processing, are more closely linked to underlying neural circuitry and provide a useful framework for investigating mechanisms using behavioural, computational, and neuroimaging methods. This thesis builds on these developments by testing mechanistic hypotheses with direct clinical relevance.

In this thesis, reward processing is examined as one such domain because of its close links to everyday functioning, underlying neural circuitry, and persistent depressive symptoms.

1.3 Reward Processing as a Mechanistic Framework for Depression

Reward processing provides a useful mechanistic perspective for understanding aspects of depression because reward-related processes shape how individuals learn from outcomes, pursue goals, and respond affectively to positive events in everyday life. Disruptions to these processes can therefore have negative consequences for motivation, engagement, and functional capacity, which are commonly observed in depression (Halahakoon et al., 2020; Whitton et al., 2015).

Reward-guided behaviour can be conceptualised as a sequence of interacting component processes. A useful mechanistic framework is provided by Husain and Roiser (2018) who separate motivated behaviour into underlying operations including option generation, cost-benefit valuation and selection, anticipatory preparation for action, initiation and maintenance of effort, consummatory interaction with outcomes, and learning from feedback (**Figure 1.1**). This framework is particularly useful for understanding depression because dysfunction at any stage of this sequence can lead to reduced engagement with rewarding activities and motivational symptoms, even when other components remain relatively intact.

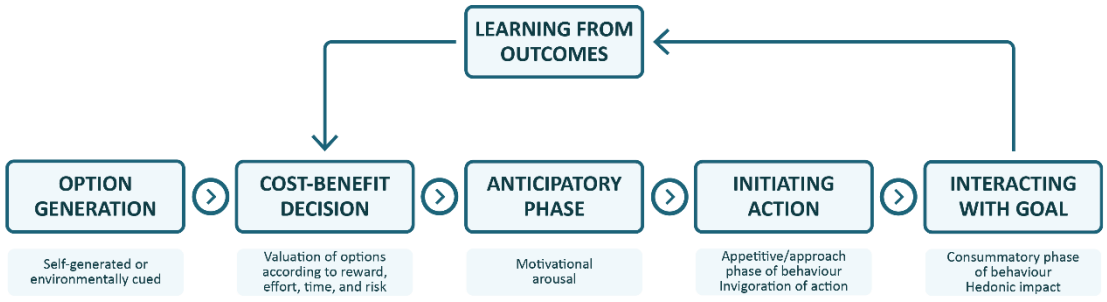


Figure 1.1 Component processes underlying reward-guided behaviour, adapted from Husain & Roiser (2018). The framework separates motivated behaviour into option generation, cost-benefit valuation and selection, anticipatory preparation, initiation and maintenance of effort, consummatory interaction with outcomes, and learning from feedback.

1.3.1 Reward Learning and Prediction Errors

Reward learning is commonly described within a reinforcement learning framework in which information about stimuli, actions, and contexts is used to predict outcomes and update expectations in order to guide behaviour (Dayan & Balleine, 2002; Glimcher, 2011; Montague et al., 1996). Learning is driven by prediction errors, a computational signal reflecting the mismatch between expected and actual outcomes (Schultz, 2016; Schultz et al., 1997).

At the neural level, prediction error signalling has been closely linked to phasic changes in midbrain dopamine activity and downstream striatal signalling (Niv & Schoenbaum, 2008; O'Doherty et al., 2006; Schultz et al., 1997; Tobler et al., 2005). These signals play a central role in learning about rewards and punishments. Positive prediction errors signal outcomes that are better than expected outcomes and tend to increase the propensity to repeat preceding actions, whereas negative prediction errors signal worse-than-expected outcomes and tend to reduce that propensity (Cox & Witten, 2019; Schultz et al., 1997).

1.3.2 Reward Anticipation

Reward anticipation occurs during the waiting period before the delivery of a reward. This phase involves forming expectations about the likelihood and value of future outcomes. Anticipatory processes are closely linked to approach behaviour and play a central role in motivating goal-directed action (Bissonette & Roesch, 2016; O'Doherty et al., 2002).

1.3.3 Motivation and Effort Expenditure

Motivation involves computing how valuable a reward is, initiating goal pursuit, and determining whether it is worth pursuing given the costs that accompany it. Effort-based decision-making captures the willingness to exert physical or cognitive effort to obtain a potential reward. These processes are central to everyday functioning and are often disrupted in depression.

1.3.4 Reward Valuation and Decision-making

Reward valuation refers to how outcomes are represented in terms of subjective value and how that value is incorporated into decisions, rather than hedonic experience ("liking"). Reward valuation has been studied using food- and monetary-based paradigms, including delay discounting and risk-based decision-making tasks (Der-Avakian & Pizzagalli, 2018).

1.3.5 Reward Outcome and Consummatory Phase

The consummatory aspect of reward reflects hedonic experience following reward receipt. In translational research, this has been assessed using paradigms such as sucrose preference in rodents and taste-based reward tasks or reward outcome phases of behavioural tasks in humans (Der-Avakian & Pizzagalli, 2018).

1.3.6 Integrating Reward Components

Deficits in reward processing can arise at multiple stages from anticipation of reward to learning from outcomes and sustaining effortful pursuit. It is therefore useful to study reward processing across stages using different methods (e.g., tasks, questionnaires, neuroimaging), while recognising that similar behavioural patterns can reflect different latent mechanisms. The reason a particular reward process was altered in some way could vary across individuals. For example, reduced reward anticipation may arise because an individual does not find the anticipated outcome sufficiently rewarding, or because predictions are inaccurate due to impairments in reward learning. These reward components rely on partially distinct behavioural and neural processes yet many studies focus on only one or two components at a time (Berridge et al., 2009). At present, it remains unclear how these processes interact, how dysfunction in one component influences others, or how treatment-related changes in one domain may exacerbate or ameliorate deficits in another.

Importantly, hedonic ("liking"), motivational ("wanting") and learning are three dissociable components of reward. Rather than liking, wanting and learning have been linked to dopaminergic

neurotransmission in the reward-network consisting of the ventral striatum and ventral tegmental area (Kumar et al., 2008). Reduced motivation to pursue rewards can occur even when consummatory pleasure is relatively intact, and vice versa (Berridge et al., 2009). This dissociation highlights the importance of isolating between reward components when characterising anhedonia and related symptoms in depression.

Anhedonia is a core feature of Major Depressive Disorder traditionally defined as reduced interest or pleasure in previously rewarding activities. Over time, this definition has expanded into a broader disruption in how individuals anticipate, value, and engage with rewarding experiences (American Psychiatric Association, 2013; Husain & Roiser, 2018; Rizvi et al., 2016). Rather than reflecting a general loss of pleasure, contemporary accounts conceptualise anhedonia as a multidimensional construct that can arise from impairments across distinct components of reward processing, including motivation, reward learning, anticipation, valuation, and consummatory experience as described above.

Anhedonia is associated with greater depression severity, poorer psychosocial functioning, and increased risk of suicidality (Ducasse et al., 2018; McMakin et al., 2012; Vrieze et al., 2013). Importantly, anhedonia has been shown to predict poorer treatment outcomes and greater likelihood of persistent or recurrent depression. Higher baseline levels of anhedonia are associated with reduced response to both pharmacological and psychological treatments and with increased risk of chronic illness course (Luca et al., 2024; Serretti, 2025; Uher et al., 2012; Vinckier et al., 2017). These findings suggest that anhedonia may reflect underlying pathophysiological processes that are not adequately targeted by first-line treatments.

Consistent with this view, converging evidence indicates that current first-line treatments for depression often show modest and inconsistent effects on anhedonia. Conventional

antidepressants, particularly SSRIs, show only modest effects on anhedonia, and improvements in positive affect and reward responsiveness are often delayed or not directly targeted (Cao et al., 2019). Clinical trials further indicate that a substantial proportion of individuals continue to experience residual symptoms following treatment, with anhedonia among the most persistent (Gaynes et al., 2009; Rush et al., 2006).

From a mechanistic perspective, limited effects of conventional antidepressants on anhedonia suggests that depression-related reward dysfunction may not be sufficiently addressed by treatments that primarily target monoaminergic systems. Rather, anhedonia is increasingly understood to reflect alterations in reward-related neural circuitry, particularly within fronto-striatal systems involved in motivation, learning from reward, and value-based decision-making (Der-Avakian & Markou, 2012; Treadway, 2016; Wang et al., 2021; Whitton et al., 2015). This mapping between anhedonia and reward-processing dysfunction provides a systematic framework for investigating depressive symptoms at a mechanistic level.

These findings position anhedonia as a clinically important, mechanistically informative, and therapeutically unresolved cardinal feature of depression. Understanding how specific components of reward processing contribute to anhedonia, and how these components are modulated by different antidepressant treatments is therefore central to addressing an important unmet therapeutic need.

This motivates the investigation of reward processing and its modulation by antidepressant treatments which forms the central focus of this DPhil thesis. The following sections therefore review research investigating reward-processing dysfunction in depression and then examine how conventional antidepressants and ketamine may differentially modulate these reward processes.

1.4 Reward Processing Dysfunction in Depression: Behavioural, Computational, and Neuroimaging Studies, and Outstanding Questions

1.4.1 Behavioural and Computational Studies

Behavioural studies of reward processing in depression reveal some consistent patterns alongside inconsistencies, which is unsurprising given the heterogeneity of depressive presentations and the diversity of tasks used to assess reward-related processes. Computational psychiatry has provided a valuable approach for interpreting these behavioural findings by disentangling latent cognitive processes underlying observed behaviour. This approach is particularly relevant given that similar behavioural impairments may arise from distinct underlying mechanisms, including alterations in learning rates, reward sensitivity, or decision policies, which are examined throughout this DPhil thesis.

Across paradigms, one of the most consistently reported findings is reduced sensitivity to rewarding outcomes and, in some tasks, heightened sensitivity to losses (Eshel & Roiser, 2010). However, the strength and presence of these effects vary across studies and reward subcomponents. A recent meta-analysis confirms small-to-moderate behavioural impairments across reward-processing tasks in depression, with effect sizes differing by reward component and task design. Notably, blunted reward bias was the most consistently associated with major depressive disorder (Halahakoon et al., 2020).

Reward processing has been examined in both medicated (Chase et al., 2010; Murphy et al., 2003; Vrieze et al., 2013) and unmedicated individuals with depression (Admon & Pizzagalli, 2015; Pizzagalli et al., 2009; Rothkirch et al., 2017), which may contribute to divergent findings. Importantly, this variability is clinically relevant, as the majority of individuals with depression receive pharmacological treatment, making medicated samples particularly representative of

clinical populations. In medicated individuals, there have been reports of reduced reward responsiveness and impaired reward learning (Vrieze et al., 2013). In the same study, reduced reward learning prior to treatment was associated with a continued diagnosis of depression eight weeks later, even after controlling for baseline symptom severity. This suggests that impairments in reward learning may be linked to illness persistence or poorer treatment response. However, such impairments are not observed consistently across studies (Chase et al., 2010; Rothkirch et al., 2017), and in some contexts reward-learning performance appears more closely related to individual differences in anhedonia than to diagnostic status. For example, Chase et al. (2010) reported that greater anhedonia severity correlated negatively with learning-rate parameters, suggesting reduced trial-by-trial behavioural adaptation in those with more severe anhedonia. The effects of antidepressant medication on reward and punishment learning are discussed in more detail in Section 1.7.

In unmedicated individuals, several studies report reduced selection of rewarding stimuli when compared to healthy controls, consistent with impaired reward learning (Admon et al., 2017) and reduced reward responsiveness (Pizzagalli et al., 2009). Reduced response bias has also been observed in remitted depression (Pechtel et al., 2013). Depression has further been associated with reduced willingness to exert effort for reward, particularly for high-reward and high-cost options (Rizvi et al., 2016; Treadway et al., 2012).

Importantly, alterations in reward learning do not always reflect deficits in learning per se, and may instead arise from changes in outcome sensitivity or value representation (Huys et al., 2013). In addition, some aspects of motivated behaviour may appear relatively intact in subsets of unmedicated individuals with moderate depression, depending on task demands and measurement sensitivity (Moutoussis et al., 2018).

Differences across studies may also reflect variation in the reward domain that is being measured, as abnormalities in reward processing may differ for monetary, social, or affective rewards; adding further complexity to the interpretation of task findings (Zhang et al., 2022). Despite such variability, converging evidence supports the presence of reward-processing abnormalities in depression at the group level, with impairments evident across learning, valuation, and effort-based decision-making domains.

Recent findings have also provided evidence of aberrant effort-based decision-making in depression. For example, studies using physical effort paradigms have shown that individuals with depression fail to increase effort expenditure as reward value increases (Cléry-Melin et al., 2019). More recent work using the Apples Gathering Task reported reduced willingness to exert effort in depressed groups (Valton et al., 2025) and in individuals with Parkinson's Disease and comorbid depression (Costello et al., 2025). Computational analyses suggested that these differences were driven primarily by reduced effort-acceptance bias rather than altered effort or reward sensitivity (Valton et al., 2025), highlighting the value of computational approaches for distinguishing between candidate mechanisms.

Overall, computational modelling studies have identified subtle reward behaviour that might otherwise be masked without it. Computational modelling has in some studies suggested that depression could be more a reward sensitivity deficit with learning seen as relatively intact, although these findings are not consistent across all studies. Using latent parameters such as learning rates, reward sensitivity, and decision thresholds can help disentangle subtle impairments in a disorder that is heterogeneous with various differences in impact across individuals and reward components. These behavioural and computational findings highlight the need to examine neural reward circuitry to better understand the mechanisms underlying reward-related deficits in depression.

1.4.2 Functional Neuroimaging Studies

Functional neuroimaging studies of reward processing in depression most consistently report abnormalities within fronto-striatal circuitry, particularly the ventral striatum, alongside orbitofrontal and medial prefrontal regions. Across two separate meta-analyses, individuals with depression show reduced striatal responses during reward processing (Keren et al., 2018; Ng et al., 2019; Zhang et al., 2013). However, the mechanistic specificity of these effects remains limited as many studies vary in reward components measured, task phase (e.g., anticipation vs outcome), medication status, making it difficult to determine which reward computations are most consistently disrupted.

The earliest meta-analysis by Zhang et al. (2013) demonstrated striatal hypo-responsivity across a wide range of reward tasks, including monetary and social rewards, and across samples varying in medication status and illness phase. While this broad inclusion supports the robustness of striatal abnormalities, it limits conclusions regarding which specific reward components such as anticipation versus outcome processing are most consistently disrupted.

Keren et al. (2018) extended this work by focusing on instrumental reward paradigms requiring trial-by-trial action-outcome learning thereby increasing mechanistic relevance to reinforcement learning processes. This meta-analysis reported particularly reduced striatal activation during reward feedback. However, the inclusion of both reward and punishment neuroimaging contrasts, and the inconsistent separation of anticipation and outcome phases across studies, makes it difficult to isolate neural responses reflecting reward valence versus salience.

Ng et al. (2019) applied a more stringent analytic approach and found distinct abnormalities within reward circuitry, including reduced ventral striatal responses alongside increased orbitofrontal cortex activation. This pattern suggests circuit-level imbalance rather than an overall

hypoactivation. Importantly, this meta-analysis noted that collapsing across reward components, task phases, mood states, medication status, and comorbidities may obscure more specific neural representations of reward valence and salience. As a result, while convergent abnormalities are evident, the precise computational and functional interpretation of these neural signals remains unresolved.

Computational neuroimaging studies further demonstrate altered reward prediction error signalling within striatal and prefrontal regions, with reduced signalling correlating with anhedonia severity (Eckstrand et al., 2019; Rothkirch et al., 2017). However, findings are not entirely consistent as increased reward prediction error signalling has also been reported in some contexts (Kumar et al., 2008), suggesting that neural abnormalities may vary as a function of task demands, illness state, or treatment response.

To summarise, these neural findings support the presence of disrupted reward circuitry in depression, but also highlight a critical limitation of the existing literature: while meta-analyses and standard neuroimaging contrasts can identify where group differences occur, they are less able to determine which computational reward processes are disrupted, how reward and punishment signals are differentially encoded within individuals, or how these neural signatures change with antidepressant treatment. Addressing these questions requires approaches that integrate task-based neuroimaging and behavioural measures with computational modelling and investigations of antidepressant treatment.

1.4.3 Outstanding Questions in Reward Processing in Depression

Despite convergent evidence for reward-related abnormalities in depression, it remains unclear which computational mechanisms best explain observed task deficits, how reward and punishment learning differ within individuals, and how reward processes change with antidepressant treatment.

Critically, these unresolved questions directly motivate the studies presented in this thesis. Study 1 examines whether reward and loss learning deficits in depression are best explained by altered learning rates or decision processes using computational modelling, and whether these reward-processing measures are associated with antidepressant treatment status. Study 2 tests whether ketamine, a treatment with rapid antidepressant effects, selectively modulates specific reward components and whether such changes are associated with improvements in anhedonia.

1.5 Transition to Treatment Mechanisms

Ongoing deficits in reward processing and related motivational symptoms when people with depression are treated with conventional antidepressants highlight an important unmet clinical need. This motivates a treatment-focused mechanistic approach: examining how conventional antidepressants and ketamine differentially modulate reward and loss processing, and whether such changes map onto improvements in anhedonia and functional outcomes. The following sections present neurocognitive mechanistic models of antidepressant action and consider their implications for reward-related processes.

1.6 Conventional Antidepressant Models of Antidepressant Action

It is important to consider how changes in monoamines translate into improvements in core depressive symptoms, particularly the cognitive distortions associated with depression such as negative bias. Several mechanistic models have been proposed to explain how conventional antidepressants exert their therapeutic effects. Conventional antidepressants were discovered serendipitously during the 1950s, following reports that depressive symptoms improved after pharmacological increases in synaptic serotonin and norepinephrine (Delgado et al., 1999; Miller, 1996). This work contributed to the monoamine hypothesis and the subsequent development of SSRIs and noradrenergic agents (Riggs & Gould, 2021). However, the monoamine hypothesis has long been challenged and cannot fully explain depression symptomatology as evidence does not

support a model in which depressive symptoms are driven solely by reduced monoamine levels (Berman et al., 2002; Delgado, 2000; Hirschfeld, 2000; Jauhar et al., 2023; Salomon et al., 1997).

From the late 1990s and early 2000s, research increasingly shifted toward neuroplasticity models of depression and antidepressant action. While monoaminergic neurotransmission is involved in various affective, behavioural, and cognitive aspects of depression, monoamines are often conceptualised as serving a neuromodulatory role and are therefore unlikely on their own to provide a full explanation for the onset and maintenance of depressive symptoms. Instead, monoaminergic systems are thought to influence downstream cellular and circuit-level processes that are more directly implicated in depression pathology (Duman et al., 1999; Manji et al., 2001).

Within this model, stress and depression are increasingly conceptualised as disorders involving impaired neural plasticity rather than solely as disorders of neurotransmitter depletion. Preclinical studies using chronic stress models have demonstrated structural and synaptic changes within cortico-limbic circuits, including dendritic retraction and reductions in dendritic spine density in the medial prefrontal cortex and hippocampus. These alterations are associated with behavioural phenotypes relevant to depression (Duman & Li, 2012; Flint & Kendler, 2014; Radley et al., 2006). Exposure to stress induces dendritic spine loss and reduced dendritic complexity in medial prefrontal cortex pyramidal neurons (Radley et al., 2006), and promotes dendritic regression and spine loss in hippocampal neurons following chronic stress exposure (Chen et al., 2008). Impairments in neural plasticity within cortico-limbic circuits are proposed to contribute to persistent patterns of negative affective and cognitive bias by limiting the ability to update maladaptive responses to emotional information (Price & Duman, 2020).

Consistent with this account of reduced plasticity, chronic stress has further been associated with reductions in adult hippocampal neurogenesis (Mirescu & Gould, 2006), whereas chronic

antidepressant treatment has been shown to increase hippocampal cell proliferation and neurogenesis (Malberg et al., 2000). This pattern supports the broader view that antidepressant efficacy may involve indirect effects on synaptic and circuit plasticity within relevant neural circuits. Within this neuroplasticity model, restoration of synaptic and circuit function is often proposed as a pathway through which conventional antidepressant treatments exert clinical effects. Conventional antidepressants are therefore thought to modulate plasticity-related processes gradually over time, consistent with the delayed onset of therapeutic benefit observed in clinical treatment.

However, this framework does not fully specify how such circuit-level changes give rise to changes in cognition and mood. A more recent model is the cognitive neuropsychological model, which proposes that conventional antidepressants act early on affective information processing, particularly negative information and that mood improves indirectly over time as these biases shift and individuals re-engage with their environment (Godlewska & Harmer, 2021; Harmer et al., 2017; Harmer, Goodwin, et al., 2009; Harmer, O'Sullivan, et al., 2009). While direct pharmacological effects, such as serotonin transporter blockade, occur rapidly, clinically meaningful mood change typically emerges over weeks. This delay may reflect the need for early changes in emotional processing to interact with ongoing experience in order to translate into symptom improvement. This model is consistent with work showing early shifts in emotional processing that precede later mood improvement (Godlewska et al., 2016). Environmental factors may also play a role, as changes in affective bias may require a recalibration of everyday interactions and learning processes.

These models suggest that antidepressants may influence depressive symptoms by altering negative cognitive and affective bias, including biases related to reward and punishment processing.

However, evidence regarding how conventional antidepressants target reward processing remains mixed, motivating further investigations across distinct reward-processing domains.

1.7 Effects of Antidepressants on Reward and Punishment Processing

There have been a small number of studies that investigate the effects of conventional antidepressants on reward and punishment processing.

Reinforcement learning provides a useful framework for investigating these effects, as it links neuromodulatory systems to learning from reward and punishment. Pharmacological studies in healthy participants indicate that short-term SSRI administration can reduce reward learning while enhancing punishment learning, or reduce sensitivity to both positive and negative outcomes (Michely et al., 2022; Palminteri et al., 2015; Scholl et al., 2017). Consistent with this, 7-day SSRI administration in healthy volunteers has been shown (computationally) to increase learning from punishment and reduce learning from reward (Michely et al., 2022). Recent work suggests increased serotonin may reduce outcome sensitivity to losses (Colwell et al., 2024), highlighting the complexity and context-dependence of serotonergic effects.

Studies examining reinforcement learning in medicated and unmedicated individuals with depression have reported impaired task performance, particularly among individuals with high levels of anhedonia (Chase et al., 2010). However, the specific mechanisms underlying these impairments remain unclear. Serotonin has been proposed to play a key role in processing aversive outcomes, raising the possibility that antidepressant-related increases in serotonin may differentially affect learning from punishment rather than restoring reward sensitivity (Mkrtchian et al., 2025). From this perspective, changes in reward-related behaviour following antidepressant treatment may reflect altered processing of aversive information rather than direct enhancement of reward function.

Overall, the evidence regarding the effects of conventional antidepressants on reward processing is mixed. It remains unresolved whether observed behavioural changes primarily reflect alterations in learning rates, outcome sensitivity, motivational processes, or interactions between reward and punishment systems. Clarifying these mechanisms is critical for understanding why reward-related symptoms such as anhedonia often persist despite treatment.

These findings motivate consideration of treatments with distinct mechanisms and temporal profiles, such as ketamine.

1.8 Ketamine and the Reframing of Antidepressant Mechanisms

The discovery that ketamine produces rapid antidepressant effects marked a major shift in how depression and its treatment are understood. Ketamine is a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist that has been used for decades as a clinical anaesthetic. In the early 2000s, a randomised double-blind, placebo-controlled study demonstrated that a single subanaesthetic intravenous infusion of ketamine (0.5 mg/kg) was associated with significant reductions in depressive symptoms within 72 hours (Berman et al., 2000). Subsequent work extended these findings to treatment-resistant depression, with a randomised, placebo-controlled, double-blind trial reporting symptom improvement from as early as 40 minutes post-infusion through to seven days (Zarate et al., 2006). Later research has consistently supported ketamine's rapid antidepressant effects, while also indicating that durability is often limited and relapse is common in the absence of repeated dosing or maintenance strategies (Kryst et al., 2020; Marcantoni et al., 2020; Murrough et al., 2013; Phillips et al., 2020; Smith-Apeldoorn et al., 2022).

Despite this clinical progress, ketamine's antidepressant mechanism of action remains unclear, and multiple explanatory models have been proposed across molecular, cellular, circuit-level, and neurocognitive domains.

A widely supported account proposes that ketamine's antagonism of NMDARs on inhibitory interneurons leads to transient cortical disinhibition and a surge in glutamatergic neurotransmission. This glutamate release is thought to drive increased α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor) throughput, with evidence indicating that AMPA-mediated signalling is required for ketamine's antidepressant effects and, in some cases, those of its metabolites (Aleksandrova et al., 2017; Maeng et al., 2008). However, the necessity of direct NMDAR inhibition for ketamine's rapid antidepressant action remains debated, particularly in light of evidence that certain ketamine metabolites may produce antidepressant-like effects in the absence of significant NMDAR blockade (Autry et al., 2011; Fukumoto et al., 2019; Zanos & Gould, 2018)

There is compelling evidence that AMPAR-dependent increases in brain-derived neurotrophic factor (BDNF)-TrkB signalling are essential for ketamine's antidepressant-like effects. Ketamine has been shown to initiate rapid synaptogenic processes within prefrontal-limbic circuits (which are affected in depression) via AMPAR-dependent increases in BDNF release and subsequent activation of TrkB-mTOR signalling pathways (Lepack et al., 2015, 2016; Li et al., 2010; Li & Wolf, 2011). These molecular and cellular changes are consistent with evidence for rapid ketamine-induced plasticity within neural circuits implicated in mood regulation, observed alongside acute clinical improvements (Kang et al., 2022; Riggs & Gould, 2021; Zanos & Gould, 2018).

Beyond synaptic plasticity mechanisms, ketamine also modulates the excitability of GABAergic interneurons and reorganises both local and long-range network dynamics. Emerging evidence suggests that these effects may involve coordinated interactions between neuronal and non-neuronal mechanisms, including glial signalling and neuromodulatory processes, which together shape circuit-level responses to ketamine (Castanheira et al., 2025; Kang et al., 2022; Matveychuk et al., 2020).

These mechanisms are increasingly viewed as interacting processes that influence neural circuit function instead of competing explanations. However, the extent to which these cellular-and circuit-level changes fully account for the cognitive and behavioural effects observed following ketamine treatment in individuals with depression remains an open question.

At the neurocognitive level, it has been proposed that ketamine may exert rapid antidepressant effects by altering the updating of negative beliefs and previously acquired maladaptive memories, potentially reducing negative bias (Costi et al., 2025; Stuart et al., 2015).

This neurocognitive account offers a potential bridge between synaptic plasticity and changes in behaviour. However, the mechanisms through which such plasticity-related changes translate into well-defined changes in cognition, behaviour, and mood remain unclear, as current evidence is largely indirect (Bottemanne et al., 2022; Costi et al., 2025; Krystal et al., 2024). This perspective is broadly consistent with ketamine's pharmacological profile as NMDAR antagonism is known to interfere with NMDAR-dependent forms of Hebbian plasticity (Krystal et al., 2024). It has also motivated experimental work suggesting that ketamine may disrupt the reconsolidation of maladaptive memories, including trauma-related memories in post-traumatic stress disorder and addiction, as well as in preclinical models (Das et al., 2019; Keizer et al., 2020). However, the extent to which such memory-related mechanisms contribute to antidepressant efficacy in major depressive disorder remains an open question.

In relation to reward processing, it remains unclear which specific components, such as anticipation, valuation, effort expenditure, or reward learning are directly modulated by ketamine and which may improve secondarily through broader shifts in affective or cognitive processing. Addressing this gap will require targeted behavioural and computational approaches capable of

isolating distinct reward processing components and linking them to underlying neurobiological mechanisms.

To summarise, recent research indicates that ketamine's antidepressant effects are being triggered by NMDAR antagonism alongside a broader set of AMPA-dependent, neurotrophic, circuit-level, and neurocognitive processes. This view has highlighted the importance of rapid plasticity-related mechanisms in antidepressant action, in contrast to slower monoaminergic effects.

1.9 Ketamine and Reward Processing

In addition to its rapid antidepressant effects on overall depressive symptoms, recent studies suggest that ketamine may be particularly effective in ameliorating anhedonia, a core feature of depression. Several studies have shown that ketamine reduces anhedonia independently of changes in overall depression severity, providing evidence for relatively specific anti-anhedonic effects (Lally et al., 2014; Murrough et al., 2013). Given that anhedonia is closely linked to dysfunction within reward-processing systems, these findings raise the possibility that ketamine exerts its therapeutic effects, at least in part, through modulation of reward-related mechanisms.

Neuroimaging studies provide further evidence linking ketamine's antidepressant effects to reward-related circuitry. Ketamine administration has been associated with increased glucose metabolism (Lally et al., 2014) and altered functional connectivity in regions implicated in reward processing, particularly the ventral striatum and nucleus accumbens (Kotoula et al., 2022; Taraku et al., 2024). These regions play a central role in encoding reward value, supporting motivation, and guiding goal-directed behaviour. Changes in striatal function following ketamine therefore provide a plausible neural substrate for improvements in anhedonia and motivational symptoms.

Despite these promising findings, much of the existing literature on ketamine and reward processing have used self-report measures of anhedonia or resting-state neuroimaging. As a result,

it remains unclear which specific components of reward processing are affected by ketamine and how these changes relate to task-based behavioural performance. For example, improvements in anhedonia could reflect enhanced reward sensitivity, altered learning from positive or negative outcomes, increased willingness to expend effort, or changes in how reward-related information is integrated during decision-making.

One task-based neuroimaging study by Kotoula et al. (2022) examined the effects of ketamine on reward anticipation and outcome processing approximately two hours following infusion. The researchers reported ketamine-related changes in activity within reward-related brain regions, most prominently during the reward outcome phase, in the absence of concurrent changes in depressive symptoms. These findings suggest that ketamine can alter reward-related neural processing prior to observable clinical improvement, supporting a mechanistic account in which early cognitive or neural changes precede later symptom change.

However, although this study provides important mechanistic insight, it focused exclusively on reward processing and did not examine learning from losses, which is also disrupted in depression and may be differentially modulated by treatment. This highlights the need for more comprehensive mechanistic approaches that examine how ketamine affects multiple components of reward processing, including both reward and loss learning, and how these changes relate to rapid symptom improvement.

1.10 Comparing Conventional Antidepressants and Ketamine: Implications for Reward Processing

Conventional antidepressants and ketamine differ in mechanism, timescale, and predicted effects on reward processing, making their comparison informative for understanding persistent reward-related symptoms in depression. Conventional antidepressants, developed from the monoamine

hypothesis, primarily increase synaptic serotonin and noradrenaline with downstream cognitive and plasticity-related effects developing gradually over time. In contrast, ketamine rapidly increases glutamatergic signalling and modulates plasticity-related processes, with clinically meaningful symptom change occurring within hours to days.

From a reward-processing perspective, serotonergic antidepressants are proposed to exert their effects indirectly through changes in affective bias and learning, particularly in relation to negative information (Harmer et al., 2009, 2017). Within a reinforcement-learning framework, this may be expressed as altered punishment learning or reduced sensitivity to negative outcomes, rather than a direct improvement of reward sensitivity or motivation. This is consistent with clinical observations that reductions in negative affect often precede improvements in positive affect and anhedonia (Harmer et al., 2009).

By contrast, ketamine's rapid plasticity-promoting effects and engagement of cortico-striatal circuitry raise the possibility that it may more directly influence specific components of reward processing, including reward anticipation, valuation, effort expenditure, or reward learning. However, the specificity of these effects remains unclear due to the limited number of task-based behavioural and computational studies.

To summarise, these differences motivate testable predictions. If conventional antidepressants primarily modulate aversive processing, treatment-related changes may be more evident in punishment learning or loss sensitivity, with modest or inconsistent effects on reward-related behaviour. Conversely, if ketamine engages reward circuitry more directly, it may produce detectable changes in specific reward components, potentially on a rapid timescale and in association with reductions in anhedonia.

1.11 Aims and Hypothesis

The aim of this thesis is to characterise alterations in reward processing that are associated with depression and to examine how conventional antidepressant treatments and the rapid-acting antidepressant ketamine modulate these processes. A range of behavioural, computational, neuroimaging, and clinical approaches are used to investigate the mechanisms underlying reward-related impairments in depression and their role in treatment response.

The thesis includes two studies: an observational study and an experimental medicine study.

Chapter 2 presents findings from Study 1, a large observational study, including a subset of participants with a clinical diagnosis of Major Depressive Disorder. This chapter examines the association between depressive symptoms, anhedonia, and reward and punishment learning using a probabilistic instrumental learning task. Behavioural performance and computational modelling are used to determine whether alterations in reward processing are better explained by changes in learning rates, outcome sensitivity, or their interaction, and whether these effects differ across reward and loss conditions. The chapter also examines whether antidepressant status is associated with differences in reward and punishment learning among individuals with Major Depressive Disorder.

Chapter 3 provides Study 2 methods from a placebo-controlled, double-blind experimental medicine study in individuals with treatment-resistant depression, in which participants were randomised to receive ketamine (0.5 mg/kg) or placebo**. Chapters 4, 5 and 6** report findings from this study. Across these chapters, task-based measures of reward processing are examined alongside self-report and clinician-rated measures of depression and anhedonia at baseline, 24 hours, and 7 days following infusion. Particular emphasis is placed on the 24-hour time point, a

well-established window during which ketamine's antidepressant effects are evident while acute dissociative effects are no longer present.

Chapter 4 focuses on clinical outcomes assessed using self-report and clinician-rated questionnaires, administered at baseline, 24 hours, and 7 days post-infusion. This chapter examines changes in overall depressive symptoms and specific domains relevant to reward dysfunction, including anhedonia, motivation, libido, and rumination. It was hypothesised that ketamine would lead to greater reductions in depressive symptoms across these domains over time compared to placebo, providing clinical context for the neurocognitive findings reported in later chapters.
These studies aim to advance mechanistic understanding of reward dysfunction in depression and to clarify how different antidepressant treatments engage reward-related processes. These findings may help inform the development of treatments that more effectively address persistent reward-related symptoms in depression.

Chapter 5 investigates the effects of ketamine on reward circuitry during a reinforcement learning task using fMRI, behavioural measures, and computational modelling 24 hours post-infusion. It was hypothesised that ketamine would alter neural responses to reward and loss outcomes within reward-related brain regions. These effects were expected to be accompanied by modulation of reinforcement learning signals, including prediction error-related responses within fronto-striatal and salience-related circuitry, relative to placebo.

Chapter 6 examines the acute and delayed effects of ketamine on motivation for reward and effort using the Apples Gathering Task, assessed 30 minutes and 7 days post-infusion. It was hypothesised that ketamine would produce acute increases in motivated decision-making that would persist at the delayed time point. Specifically, ketamine was expected to increase reward sensitivity and reduce sensitivity to effort costs, resulting in greater willingness to accept high-

reward, high-effort options and reduced reaction time on trials with higher reward, compared to placebo.

These chapters examine reward impairments in depression across observational and experimental medicine studies, linking behavioural measures, computational modelling, neural mechanisms and clinical methods.

Chapter 2: Study 1: The Association of Conventional Antidepressants on Reward Processing

Introduction

As outlined in Chapter 1, reward processing involves a range of cognitive operations through which information about rewarding and aversive outcomes is used to guide behaviour. These processes are commonly conceptualised as involving motivational, hedonic and reinforcement learning components, which rely on partly distinct brain networks. Disruptions across all of these components have been consistently implicated in depression, with converging evidence suggesting that individuals with depressive symptoms exhibit alterations in reward-related behaviour.

Numerous studies have shown that individuals with MDD have aberrant processing of both reward and punishment. In particular, depression has been associated with hyposensitivity to rewards and hypersensitivity to punishments (Admon & Pizzagalli, 2015; Eshel & Roiser, 2010; McFarland & Klein, 2009; Pizzagalli et al., 2005; Robinson et al., 2012). However, findings across studies are not entirely consistent, and alterations in reward and punishment processing do not always occur together.

In probabilistic reward learning tasks, participants with MDD have been shown to display a reduced response bias towards more frequently rewarded options (i.e. the optimal choice) compared to healthy participants (Admon & Pizzagalli, 2015; Kunisato et al., 2012; Pizzagalli et al., 2008). This reduced reward bias may persist during remission and has been shown to predict poorer treatment outcomes (Pechtel et al., 2013; Vrieze et al., 2013). Other studies suggest that depression may be more reliably characterised by reduced sensitivity to positive outcomes, while evidence for increased sensitivity to negative outcomes is less consistent (Chase et al., 2010; Eshel & Roiser, 2010; Henriques & Davidson, 2000; Mukherjee et al., 2020). In contrast, some studies

have reported heightened sensitivity to punishment or greater avoidance of loss in depression (Dombrovski et al., 2013; Lemelin & Baruch, 1998; Murphy et al., 2003). However, these findings vary considerably across tasks and samples and may reflect methodological differences rather than a general alteration in punishment sensitivity. In sum, these findings indicate that while depression is associated with altered responses to reward and punishment, the direction and specificity of these effects remain inconsistent across studies. This is not surprising considering the heterogeneity of depression.

Computational modelling approaches, and reinforcement learning (RL) models in particular, have been increasingly used to separate these processes by characterising how individuals update value representations in response to feedback (Sutton & Barto, 1998). RL models have been widely applied to the study of reward processing in depression (Chen et al., 2015; Huys et al., 2013, 2015; Mukherjee et al., 2020). Some studies have reported learning-related impairments in depression, including evidence that lower reward learning rates are associated with greater anhedonia severity, although overall learning rates may not differ between depressed participants and controls (Chase et al., 2010). These findings suggest that reinforcement learning abnormalities in depression may relate more closely to reward-related symptom severity than to diagnosis alone. Consistent with this, participants with depression have been shown to perform worse than controls on reward-learning tasks, with impairments observed during both learning and decision phases (Pizzagalli et al., 2008; Rupprechter et al., 2018).

In contrast, other researchers have argued that depression is more consistently associated with reduced sensitivity to outcomes, rather than alterations in learning rates (Huys et al., 2013, 2015; Pulcu et al., 2024). From this perspective, individuals with depression may still be able to update their expectations based on feedback, but show blunted behavioural responses to rewarding outcomes. Overall, it remains unclear whether depression is characterised by alterations in learning

rates, outcome sensitivity, or both, and whether these effects differ across positive and negative outcomes.

These distinctions are particularly relevant when considering the effects of conventional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs), which are the first-line pharmacological treatment for depression. Despite their efficacy in reducing core mood symptoms, there is evidence that reward-related symptoms, including anhedonia, may not be fully ameliorated by antidepressant treatment and, in some cases, may even be exacerbated or accompanied by emotional blunting (Goodwin et al., 2017; Ma et al., 2021; McCabe et al., 2010; Uher et al., 2012).

Studies examining the effects of SSRIs on reinforcement learning have largely been conducted on healthy participants. Short-term SSRI administration has been shown to reduce reward learning while enhancing punishment learning (Michely et al., 2022), as well as to decrease sensitivity to both positive and negative outcomes (Palminteri et al., 2015; Scholl et al., 2017). More recent work has suggested that increased synaptic serotonin may reduce sensitivity to loss outcomes (Colwell et al., 2024). While these findings highlight a role for serotonin in modulating reward and punishment processing, how this interacts with depression remains uncertain.

Reinforcement learning studies including medicated and unmedicated individuals with depression have reported impaired task performance, particularly among individuals with high anhedonia symptoms (Admon & Pizzagalli, 2015; Chen et al., 2015; Vrieze et al., 2013). However, the specific mechanisms underlying these impairments remain unclear. Serotonin has been proposed to play a particular role in the processing of aversive outcomes (Crockett et al., 2015), raising the possibility that antidepressant-related increases in serotonin may differentially influence learning from reward and punishment. From this perspective, antidepressant-related changes in reward learning may, in

part, reflect altered processing of aversive outcomes or expectations, rather than direct enhancement of reward sensitivity. Such context-dependent effects may contribute to the heterogeneous behavioural findings reported across different tasks and populations.

Overall, the evidence regarding the effects of antidepressants on reward processing is mixed, and it remains unresolved whether behavioural changes primarily reflect alterations in learning rates, outcome sensitivity, or the relative rewarding and aversive outcomes. Clarifying these mechanisms is critical for understanding the persistence of reward-related symptoms in depression and the variable effects of antidepressant treatment.

Study Aims

The aim of this chapter is to examine how depressive symptoms, anhedonia, and antidepressant status are associated with reward and punishment learning using a probabilistic instrumental learning task.

Using a large online dataset collected in the context of the COVID-19 pandemic, the analyses presented aimed to do the following:

First aim is to investigate associations between depressive symptoms, anhedonia, and task performance across reward and punishment conditions.

Second aim is to focus on a subset of participants with a diagnosis of major depressive disorder, the chapter examined whether antidepressant status is associated with differences in learning and outcome sensitivity. Using behavioural and computational modelling, this chapter aimed to clarify whether alterations in reward processing in depression are better explained by changes in learning,

outcome sensitivity, or their interaction, and whether these effects differ across reward and loss conditions.

Hypotheses

H1: Greater depressive symptom severity will be associated with differences in performance on the probabilistic instrumental learning task across win (reward) and loss (punishment) conditions.

H2: Higher levels of anhedonia will be associated with differences in performance on the probabilistic instrumental learning task, particularly in win (reward) conditions.

H3: Behavioural differences in probabilistic instrumental learning associated with depressive symptom severity and anhedonia will be reflected in alterations in computational parameters indexing learning rates and/or outcome sensitivity.

H4: In MDD participants, antidepressant status will affect loss learning and/or outcome sensitivity on the probabilistic instrumental learning task.

Methods

Study Design

The Oxford COSIE study (COvid-19, Social Isolation and Emotion) was conducted online with four phases of data collection between April 2020 and February 2021 (**Figure 2.1**). The study investigated the longitudinal relationship between emotional biases during periods of social distancing associated with the COVID-19 pandemic. Across the four study visits, participants completed emotional processing tasks and reward processing was assessed at a single time point using a probabilistic instrumental learning task and questionnaires.

This chapter focuses specifically on performance on the PILT, computational modelling of task behaviour, and associated self-report measures of anhedonia and depressive symptoms. Only data from this single time point were analysed in this thesis.

All study procedures were programmed online using the Gorilla Experiment Builder platform. Participant recruitment was managed via Prolific Academic. All tasks and questionnaires were completed via a web browser supported by the Gorilla Experiment Platform. Participation was restricted to desktop or laptop computers with an internet connection, no mobile devices.

The study received ethical approval from the University of Oxford CUREC (R69299/RE001) on April 17, 2020. All participants provided informed consent prior to participation at each study visit.

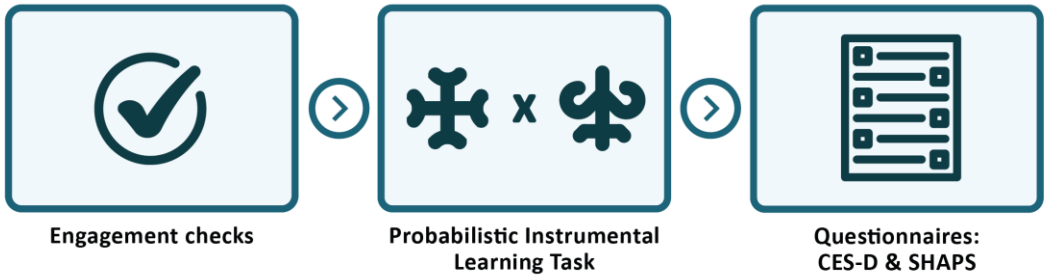


Figure 2.1 Study procedure for the Oxford COSIE study. Participants provided informed consent, completed engagement checks to ensure understanding of the task, then performed the probabilistic instrumental learning task (PILT), followed by self-report questionnaires. Abbreviations: Snaith-Hamilton Pleasure Scale (SHAPS), Center for Epidemiologic Studies Depression Scale (CES-D).

Participants and Recruitment

Participants were recruited via the Prolific Academic research participant pool. Inclusion criteria were: age 18 years or over, currently living in the United Kingdom, access to a computer with an internet connection and passing all task comprehension checks. Demographic characteristics of the analysed samples are reported in **Table 2.1.** A total of 2,043 participants were recruited as part of the main longitudinal study, with 1,917 participants included in the present analysis.

Measures

Demographic information

Participants reported current and past diagnoses of Major Depressive Disorder and current use of medication. Participants completed demographic questions via multiple-choice responses.

Questionnaires

Self-reported depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D), and anhedonia symptoms were assessed using the Snaith-Hamilton Pleasure Scale (SHAPS).

Snaith-Hamilton Pleasure Scale (SHAPS)

Anhedonia was assessed using the Snaith-Hamilton Pleasure Scale (SHAPS), a widely used self-report measure of hedonic capacity (SHAPS;Snaith et al., 1995). The SHAPS is one of the most commonly used self-report measures of anhedonia in adults with Major Depressive Disorder (MDD) and has demonstrated good internal consistency and construct validity in clinical samples (Nakonezny et al., 2010, 2015).

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The SHAPS consists of 14 items which assess the ability to experience pleasure across a range of domains, including social interaction, sensory experience and interest-based activities. Each item

is rated on a four-point Likert scale ("definitely agree", "agree", "disagree" and "strongly disagree").

Responses of "definitely agree" and "agree" are scored as 0, while responses of "disagree" and "strongly disagree" are scored as 1. Total scores range from 0 to 14, with higher scores indicating greater anhedonia severity. A score of 3 or higher indicates high level of anhedonia.

The SHAPS was selected for this study because it is brief, self-administered and well-validated in adults with MDD, making it suitable for online data collection.

Center for Epidemiologic Studies Depression Scale (CES-D)

Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D;Radloff, 1977). The CES-D is a 20-item self-report measure designed to measure the frequency of depressive symptoms experienced over the past week. Each item is rated on a four-point scale reflecting symptom frequency.

Item scores are summed to produce a total score ranging from 0 to 60, with higher scores indicating greater depressive symptom severity. The CES-D assesses a range of symptom domains including mood, sleep, appetite, guilt, loneliness, and psychomotor functioning. A total score of 16 or higher is commonly used as a cut-off for indicating clinically significant depressive symptoms; however, the CES-D is not a diagnostic tool for MDD.

The CES-D was selected for the study because it is well validated for use in large community samples and is suitable for repeated measurement across multiple time points.

Probabilistic Instrumental Learning Task (PILT)

Reward learning was assessed using the adapted probabilistic instrumental learning task (PILT;Pessiglione et al., 2006). This task measures the ability to learn stimulus-outcome

associations through trial-by-trial feedback. Probabilistic instrumental learning impairments have been consistently reported in depression, making the PILT a suitable paradigm for assessing reward-based learning processes.

The PILT is a two-arm bandit task with interleaved reward and loss trials. On each trial, participants chose between two abstract symbols associated with reciprocal outcome probabilities (0.7 vs 0.3). In the win trials, choices resulted in either a gain (20 points) or no win (0 points), whereas in loss trials choices resulted in either a monetary loss (-20 points) or no loss (0 points).

The task consisted of three blocks of 60 trials, with each block including 30 wins and 30 loss trials. Trial order was randomised within each block and the left/right position of the advantageous stimulus was randomised on every trial to ensure that spatial location was not predictive of outcome. A schematic of the task is shown in **Figure 2.2**.

Before the beginning of the task, participants completed an engagement check consisting of multiple-choice questions assessing understanding of the task and stimulus-outcome contingencies. Participants were required to answer all questions correctly before starting the task. Participants were informed that they would begin the task with 100 points and were instructed to win as much money as possible. In order for participants to maximise their winnings, participants could use the outcome feedback to gradually learn the symbol-outcome associations over time, such that they consistently choose the symbol with the high-probability win and avoid the symbol with the high-probability loss.

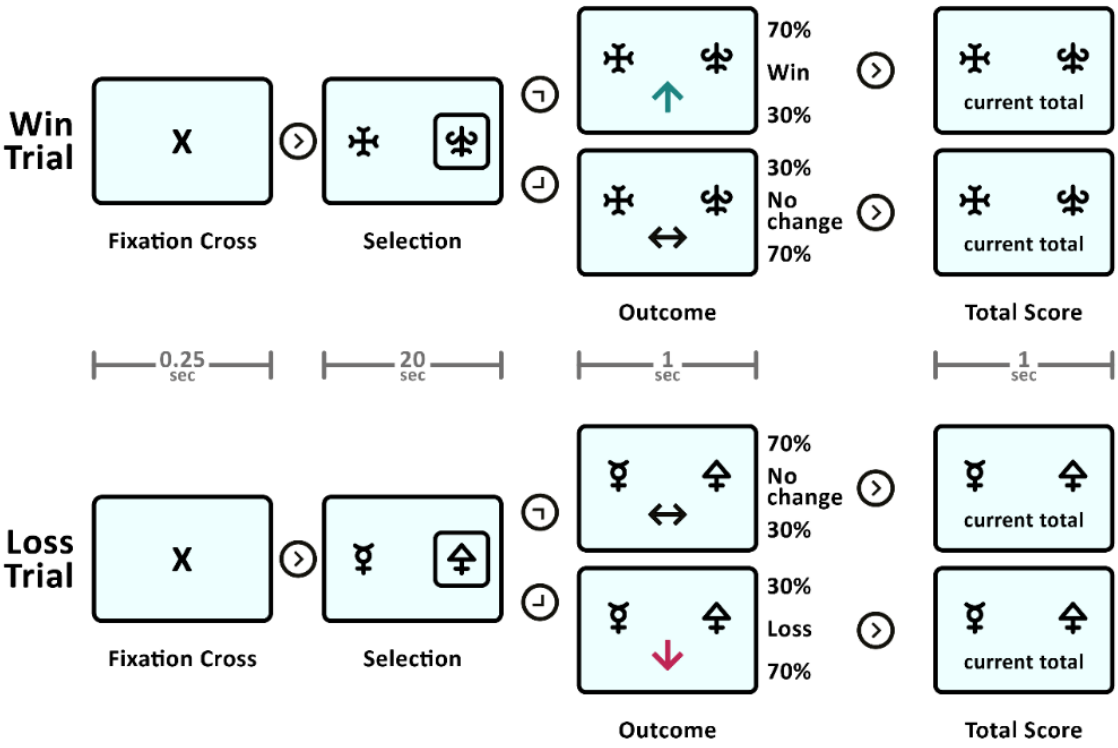


Figure 2.2 Schematic of the probabilistic instrumental learning task (PILT). On each trial, two abstract symbols were presented on the left and right of the screen, and participants selected one option using a keyboard response within a fixed response window. Following the choice, feedback indicating the trial outcome (win, loss, or neutral) and the current total earnings was displayed on screen. Win and loss trials were interleaved throughout the task.

Procedure

Participants completed the study online via Prolific Academic and Gorilla Experiment Builder within a single online session. After providing informed consent, participants completed engagement checks to ensure understanding of the task instructions and contingencies. Participants then completed the probabilistic instrumental learning task, followed by the CES-D and SHAPS questionnaires.

Behavioural Pre-processing

Raw task data was exported from Gorilla and processed in R (version 4.4.3). The original presentation order (Gorilla event sequence) was retained as a fixed sequence to ensure similar task experiences across participants. Reaction times (RTs) were converted to numeric values, and trials with RTs shorter than 200ms or longer 5000ms were excluded. Win and loss trials were analysed separately.

Behavioural summary measures used for analysis included mean reaction time, percentage correct, and the proportion of advantageous choices. Advantageous choices were defined as selection of the high probability stimulus on win trials and low probability stimulus on loss trials. Data were organised by block and for the final 20 trials of each block. Outliers were identified using a 3± standard deviations rule applied at the participant level to overall advantageous choice rate and overall mean reaction time.

Computational Modelling of Reward Learning

Data preparation for computational modelling

Behavioural data was exported from Gorilla and reorganised into trial-by-trial data format suitable for computational modelling. The original presentation order (Gorilla event sequence) was maintained to ensure that the model captured the actual randomised order for each participant.

Model specification

Choice behaviour was modelled using a Rescorla-Wagner reinforcement learning framework with two free parameters: a learning rate $\alpha = (0,1)$ and an inverse temperature, $\beta > 0$ (Rescorla & Wagner, 1972; Behrens et al., 2007). The model describes how participants update expectations about stimulus-outcome associations across trials.

Expected values were updated according to the learning rule:

$$Q_{t+1}(s) = Q_t(s) + \alpha(R_t - Q_t(s))$$

Where $Q_{t+1}(s)$ is the expected outcome probability of choosing the optimal stimulus *s* in trial *t+1*, $\propto$ is the learning rate, and R_t is the outcome of the previous trial. Expectancies were initialised at $Q_1 = 0.5$ at the start of each block.

Choice rule

Choice probabilities were calculated using a logistic (binary softmax) choice rule. The probability of selecting the advantageous stimulus on trial *t* was defined as:

$$P_t(s) = \frac{1}{1 + e^{-\beta(Q_t(s)-0.5)}}$$

where $P_t(s)$ is the probability of choosing the optimal stimulus *s* on trial *t*, β is the inverse temperature parameter, and $Q_t(s)$ is the expected outcome probability of choosing the optimal stimulus *s*.

Parameter estimation

Model parameters were estimated separately for each participant and for win trials and loss trials. Parameter estimation followed a Bayesian grid-based approach in which the likelihood of observed choices was evaluated across a range of learning-rate and inverse-temperature values to derive posterior probability distributions over parameters. Missed trials were excluded from the likelihood, and parameter transformations were applied to ensure that learning rates were bounded between 0 and 1 and inverse-temperature values remained positive. Final parameter estimates were summarised as probability-weighted averages of the marginal posterior distributions.

Statistical Analysis

Model-free Analysis

Choice accuracy was defined as the proportion of trials on which the participant selected the optimal stimulus (i.e. the stimulus associated with a 0.7 probability of winning in win trials and 0.7 probability of avoiding loss in loss trials).

Choice accuracy was analysed using mixed ANOVAs with valence (win vs loss) as a within-subject factor. Depressive symptoms (CES-D) and anhedonia symptoms (SHAPS) were entered into separate models as continuous predictors. All trials and the last 20 trials were analysed to estimate asymptotic performance after learning had plateaued.

For analyses restricted to participants meeting criteria for MDD, mixed ANOVAs included valence (win vs loss) as a within-subjects factor and antidepressant use (medicated vs unmedicated) as a between-subjects factor. Depressive symptoms (CES-D) and anhedonia symptoms (SHAPS) were again entered separately as continuous predictors.

Model-based Analysis

Model-based analyses followed the same statistical plan as the model-free analyses but used computational parameters as dependent variables. Specifically, learning rate and inverse temperature parameters were analysed separately using mixed ANOVA models with valence (win vs loss) as a within-subjects factor and symptom measures (CES-D or SHAPS) or antidepressant status as predictors, as described above.

Results

	All participants (n=1917)
Age	45.50 (14.29)
Female /Male/NB, n	1,133/779/4
CES-D score	16.75 (12.27)
SHAPS score	2.07 (2.95)

Table 2.1 Demographic and symptom scales for all participants. Values are presented as mean ± SD, except where noted. Higher scores on the CES-D indicate greater depressive symptom severity. SHAPS higher scores indicate greater anhedonia.

Task Performance

Across all participants, there was a significant main effect of valence on optimal choice accuracy [$F(1, 1916) = 18.14$, $p < 0.01$] with participants making more optimal choices during win trials [$M = 68.17$, $SD = 18.22$] than during loss trials [$M = 66.24$, $SD = 12.79$]. This was consistent for the last 20 trials [$F(1, 621) = 5.28$, $p = 0.02$].

There was also a significant effect of valence on the learning rates [$t(1916) = -20.26$, $p < 0.01$] and inverse temperature parameters [$t(1916) = 35.66$, $p < 0.01$]. Learning rates differed by valence with higher learning rates during loss trials [$M = 0.24$, $SD = 0.20$] relative to win trials [$M = 0.13$, $SD = 0.14$]. In contrast, inverse temperature parameters differed in opposite direction with higher inverse temperature values during win [$M = 19.31$, $SD = 14.49$] than loss trials [$M = 7.29$, $SD = 9.96$].

Associations between depressive symptoms, anhedonia, and task conditions

There was no significant CES-D x valence interaction on optimal choice behaviour [$F(1, 1914) = 1.95, p = 0.16$]. Similarly, no significant SHAPS x valence interaction was observed [$F(1, 1899) = 0.23, p = 0.63$]. There were no significant main effects of CES-D [$F(1,1914)=2.17$, p=0.14] or SHAPS [$F(1, 1899)=1.95, p = 0.16$] on optimal choice behaviour.

Analyses restricted to the final 20 trials showed a similar pattern. There was no significant main effect of CES-D [$F(1, 1621) = 3.33, p = 0.07$] or SHAPS [$F(1, 1621) = 2.24, p = 0.13$] on optimal choice, no significant CESD x valence interaction [$F(1, 1621) = 1.85, p = 0.17$] or SHAPS x valence interaction [$F(1, 1607) = 0.44, p = 0.51$].

In contrast, a significant CES-D x valence interaction was observed on learning rate [$F(1, 3828) = 5.50, p = 0.02$]. Follow-up simple slopes indicated that higher CES-D scores were associated with lower learning rates during loss trials [$t(3828) = -2.17, p = 0.03$], whereas no association was observed for win trials [$t(3828) = 0.99, p = 0.32$]. This pattern is displayed in **Figure 2.3**. There was no CESD x valence interaction observed for inverse temperature [$F(1, 3828) = 1.76, p = 0.19$].

Anhedonia, as measured by SHAPS scores was not significantly associated with any computational parameter. Specifically, no SHAPS x valence interaction was observed for learning rate: [$F(1, 3798) = 0.76, p = 0.38$] or inverse temperature: [$F(1, 3828) = 0.004, p = 0.95$].

Overall, these findings suggest that higher levels of self-reported depression, but not self-reported anhedonia, were selectively associated with reduced loss learning rates.

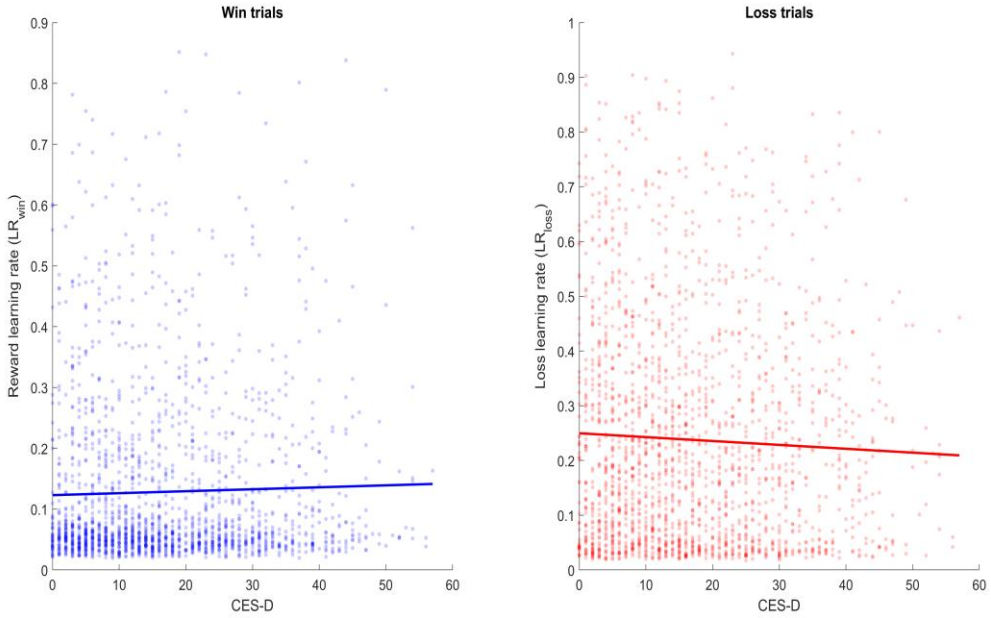


Figure 2.3 Higher depressive symptoms were significantly associated with lower learning rates for loss trials. Individual data points show participants' learning rates for win (blue) and loss (red) trials plotted against CES-D scores; solid lines represent model-estimated trends. No significant association was observed for win trials.

Association between antidepressant status and task performance in MDD participants

Participants

Medicated [$N = 124$] and unmedicated [$N = 55$] participants with MDD did not differ significantly in CES-D scores, [$t(118.9) = -1.08$, $p = 0.28$], or SHAPS scores, [$t(100.6) = -1.29$, $p = 0.20$], indicating comparable levels of depression and anhedonia severity across medication groups **(Table 2.2).** However, there was a significant difference in age between groups, which was therefore included as a covariate in subsequent analyses.

	Medicated group $N = 124$	Unmedicated group $N = 55$	p - value
Age	42.23 (13.39)	33.38 (12.97)	<0.01
Female /Male/NB	83/40/1	33/21/1	0.60
CES-D score	28.11(13.15)	30.20 (11.39)	0.28
SHAPS score	4.20 (4.20)	5.11 (4.37)	0.20
SSRI use, n (%)	67.74%	-	-

Table 2.2 Demographic and symptom scales of the MDD participants. Values are presented as mean ± SD, except where noted. Higher scores on the CES-D indicate greater depressive symptom severity. SHAPS higher scores indicate greater anhedonia. A score of ≥ 3 indicates high level of anhedonia.

There was a significant antidepressant x valence interaction for optimal choices [$F(1, 293) = 5.56$, $p = 0.02$] and this remained when looking at the last 20 trials [$F(1, 293) = 5.44$, $p = 0.02$]. Post-hoc tests showed that participants taking antidepressants made significantly fewer optimal choices during loss trials compared with unmedicated participants [$F(1, 145) = 5.96$, $p = 0.02$]. There was no significant group difference was observed during win all trials [$F(1, 145) = 1.40$, $p = 0.24$] or in the last 20 trials [$F(1, 145) = 0.66$, $p = 0.4$] **(Figure 2.4).** These findings remained significant after controlling for age, depressive symptoms (CES-D), and anhedonia (SHAPS) and for the last 20 trials [$F(1, 145) = 5.28$, $p = 0.02$]. Medicated participants were more likely to select the high-probability stimulus during loss trials. Learning curves illustrating these group differences are shown in **(Figure 2.5).**

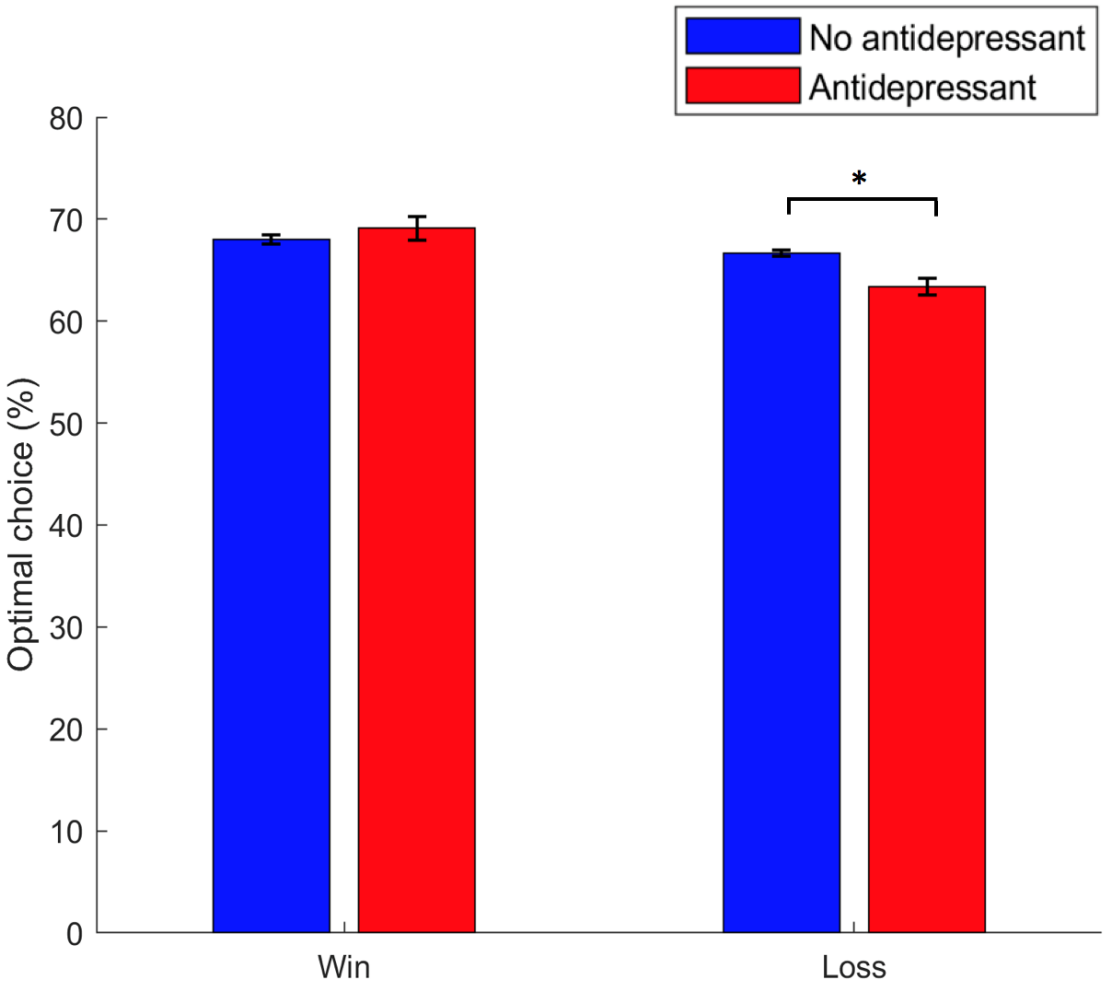


Figure 2.4. Participants taking antidepressants made significantly fewer optimal choices during loss trials compared with unmedicated participants. Bars show group means for win and loss trials, with error bars indicating standard error of the mean (SEM). *$p < 0.05$.

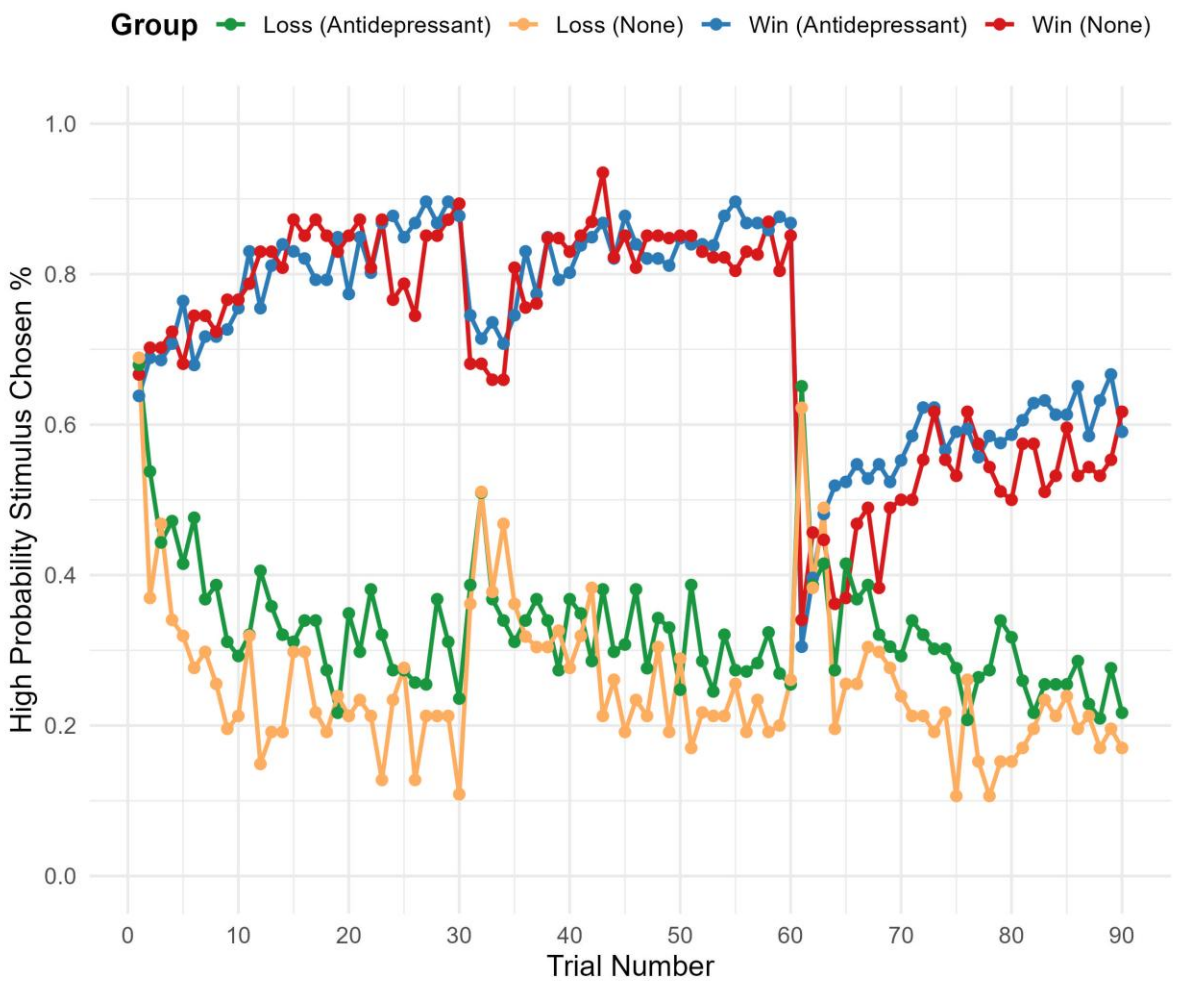


Figure 2.5. Learning curves across all 90 trials depicting choice accuracy during win and loss trials in participants taking antidepressants and unmedicated participants. The mean probability of selecting the high-probability stimulus is shown separately for win and loss trials. In win trials, the high-probability stimulus is associated with wins, whereas in loss trials it is associated with a higher probability of loss (i.e., the non-optimal option). The task consisted of three blocks of 30 trials, with different stimulus pairs presented in each block.

A significant antidepressant x valence interaction was also observed for learning rate [$F(1, 354) = 6.56$, $p = 0.01$] (**Figure 2.6**). Participants taking antidepressants had a significantly higher learning

rates for loss trials [$t(354) = 3.24$, $p < 0.01$] compared with unmedicated participants, whereas no significant group difference was observed for win trials [$t(354) = 0.30$, $p = 0.76$].

Similarly, a significant antidepressant x valence interaction was observed for the inverse temperature parameter [$F(1, 354) = 3.75$, $p = 0.05$]. During loss trials, the antidepressant group had a significantly lower inverse temperature [$t(354) = -2.54$, $p = 0.01$]. However, no significant group differences were observed for inverse temperature during win trials [$t(354) = -0.33$, $p = 0.74$]. These results are illustrated in **Figure 2.6** which presents loss learning rates (**Figure 2.6A**) and loss inverse temperature parameters (**Figure 2.6B**) separately for medicated and unmedicated participants with MDD.

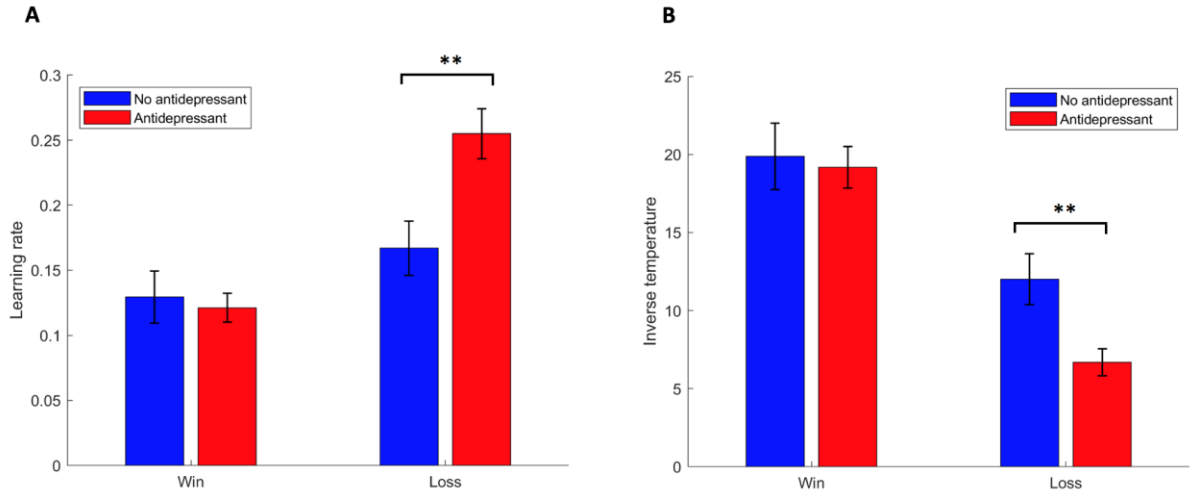


Figure 2.6. Antidepressant-associated differences in reinforcement learning parameters. Reinforcement learning models were fitted to participant choice data; with parameters estimated for learning rate and inverse temperature. **(A)** Learning rates for wins and losses; participants taking an antidepressant have a significantly higher learning rate for loss trials. **(B)** Inverse temperature for win and losses; participants taking antidepressants showed a significantly lower inverse temperature for loss trials compared with unmedicated participants. ** $p < 0.01$.

Overall, these findings indicate that antidepressant use in MDD is associated with altered learning and sensitivity specifically during the loss trials, independent of depressive symptom severity and anhedonia as measured by the CES-D and SHAPS.

Discussion

The study examined how depressive symptoms, anhedonia and antidepressant use relate to reward and loss learning using questionnaires, a reward learning task and computational modelling. The findings provide insight into the mechanisms potentially underlying altered reward processing in depression and the effects of antidepressant treatment on these processes.

The main effect of valence across the full sample and MDD participants supports the notion that reward and loss learning engage partially dissociable processes. This highlights a strength of the task and the importance to examining reward and loss learning separately.

Unexpectedly, depressive symptom severity was not associated with overall task performance, nor did it interact with valence for optimal choice behaviour. However, computational modelling revealed a more nuanced pattern. Specifically, greater depressive symptom severity was associated with reduced learning rates during loss trials, with no association observed for reward learning rates or inverse temperature. No interaction between depressive symptoms and valence was observed for inverse temperature. This pattern differs from some previous reinforcement-learning studies reporting heightened learning from loss and reduced learning from reward, or altered choice stochasticity, in depression (Huys et al., 2013; Pike & Robinson, 2022). However, reinforcement-learning alterations in depression are highly task- and context-dependent.

The difference between the behavioural and computational findings is important. The absence of an association between depression and task performance (choice accuracy) may suggest that these

symptoms do not generally impair overall performance as reported in other studies. Rather, the finding points to alterations in how feedback is integrated over time, particularly in response to negative outcomes (loss).

Reduced learning rates during loss trials suggest a reduced updating of value representations following negative outcomes. This may reflect a reduced impact of negative outcomes on belief updating under probabilistic feedback, rather than heightened loss sensitivity. Such differences would be difficult to detect in the absence of computational modelling, highlighting the value of computational models in isolating latent learning processes that are otherwise hidden in behaviour.

The selective association with loss learning suggests that depressive symptoms may be linked to difficulties adapting behaviour in response to negative feedback (loss), rather than impairments in reward-driven learning. Importantly, this type of alteration would not necessarily produce deficits in overall task performance. This supports the view that depression-related alterations in RL are context-dependent and may be masked at the behavioural level when learning and decision processes are conflated.

No significant associations were observed between anhedonia symptoms and either choice behaviour or computational modelling parameters. This was unexpected given prior evidence linking anhedonia to reward-processing deficits in depression (Admon & Pizzagalli, 2015). One possible explanation is that the SHAPS primarily indexes consummatory hedonic experience and may therefore be relatively insensitive to individual differences in trial-by-trial reinforcement-learning processes assessed in the PILT. In contrast, broader measures of anhedonia such as the Dimensional Anhedonia Rating Scale (DARS), which capture anticipatory and motivational

aspects of reward in addition to consummatory pleasure, may be better positioned to relate to learning-based task performance, even though they do not directly assess reinforcement learning.

Within the clinically diagnosed MDD subsample, antidepressant use was associated with significant differences in loss learning and inverse temperature. Medicated participants made fewer optimal choices during loss trials compared with unmedicated participants, an effect that remained significant after controlling for depressive symptom severity and anhedonia. Importantly, this behavioural difference was also seen in the computational parameters, including higher learning rates and lower inverse temperature values during loss trials among medicated participants. There was no significant difference observed in the win trials.

Importantly, this pattern was directionally opposite to that observed for depressive symptom severity in the larger sample, where greater symptom severity was associated with reduced loss learning rates. This contrast supports the interpretation that antidepressant-related effects reflect altered avoidance learning rather than symptom severity. Specifically, antidepressant status was associated with increased updating following negative outcomes (higher loss learning rates), alongside a reduced degree to which choices were guided by learned value differences during loss trials (lower inverse temperature).

In probabilistic instrumental learning tasks, higher learning rates are not necessarily adaptive. Strong trial-by-trial updating may instead reflect over-responsiveness to stochastic losses, leading to behavioural changes driven by random fluctuations rather than gradual integration of feedback across trials (Sutton & Barto, 1998). From this perspective, the present findings point to altered avoidance learning rather than a generalised impairment or improvement in task performance. These effects are consistent with cognitive neuropsychological models proposing that

antidepressants act early on affective and cognitive processing biases, prior to or independently of changes in mood symptoms (Harmer et al., 2017).

The loss learning differences observed in the present study are consistent with the broader view that serotonergic modulation may play a particularly prominent role in aversive or punishment-related contexts, rather than directly improving reward processing. Antidepressant-related effects were specific to loss trials, suggesting that serotonergic treatments may primarily modify how negative outcomes are integrated and used to guide future behaviour, rather than restoring typical reward sensitivity. This interpretation aligns with clinical observations that antidepressants often improve mood without fully alleviating anhedonia, and with evidence that serotonergic manipulations can differentially influence loss learning (Colwell et al., 2024).

Within the MDD-only sample, reduced choice accuracy on loss trials in the antidepressant group could be interpreted behaviourally as impaired avoidance learning. However, the RW modelling results suggest a more nuanced account. In probabilistic tasks, higher loss learning rates do not necessarily reflect more effective learning, as negative outcomes can occur even for optimal options. Strong trial-by-trial updating following losses may therefore lead individuals to adjust behaviour too readily in response to stochastic outcomes, rather than integrating feedback across trials, resulting in poorer performance despite higher estimated learning rates (Sutton & Barto, 1998). Lower inverse temperature on loss trials further indicates that choices were less consistently guided by learned value differences, suggesting increased variability in choice expression under aversive conditions.

Importantly, higher loss learning rates are not inherently maladaptive. In other contexts, increased updating following negative outcomes could reflect reduced avoidance or greater openness to learning from aversive experiences. From this perspective, the reversal of the pattern observed

with depressive symptom severity, where greater severity was associated with reduced loss learning rates is theoretically informative. Rather than reflecting impairment, antidepressant-related increases in loss learning may indicate altered engagement with negative outcomes, even if such changes appear suboptimal in the stable environment of the present task.

Importantly, these findings should be interpreted as associations rather than causal effects of medication. Differences between medicated and unmedicated participants may reflect unmeasured factors related to treatment status, such as illness history or clinical severity. Although the models controlled for depressive symptom severity and anhedonia, the associations remained significant. Nevertheless, the observed pattern is consistent with the cognitive neuropsychological model, which proposes that antidepressants change the processing of emotionally salient information, particularly negative information, and that these changes lead to subsequent improvements in mood (Godlewska & Harmer, 2021).

Given the observational nature of the study, all findings relating to antidepressant status are interpreted as associations rather than causal effects of medication. The present findings contribute to a growing body of evidence suggesting that conventional antidepressants do not fully normalise reward processing. Instead, their effects may be better described as context-dependent alterations in learning from negative outcomes. Such changes could support gradual mood improvement by modifying the impact of aversive experiences or reshaping expectations, while leaving core reward-related deficits, such as anhedonia, relatively intact. This framework may help explain why antidepressants often improve mood without fully alleviating reward-related symptoms. Within a clinical context, the results suggest that individuals taking antidepressants may show altered updating of expectations in response to negative environments, whereas motivational engagement or reward valuation may remain relatively unchanged.

Strengths and limitations

This study was observational, which meant that the participants were not experimentally controlled. Medication dose and duration were not collected and there was no matched healthy control group for comparison. In addition, there was a preference for symbols in blocks one and two of the task which may reflect practice or learning effects, with participants performing better in earlier trials. Despite these limitations, a key strength of the study was the large sample size, particularly within the MDD group which can be difficult to achieve within a clinical population.

Conclusions

In summary, the present findings suggest that alterations in reward processing in depression may be valence-specific and context-dependent, particularly in relation to learning from negative outcomes. Depressive symptom severity and antidepressant status were associated with distinct patterns of loss learning, whereas self-reported anhedonia showed no clear relationship with choice accuracy or reinforcement-learning parameters. By separating learning from choice behaviour, these results highlight the value of computational approaches for understanding reward-processing impairments in depression and complexity of antidepressant-related differences.

Chapter 3: Study 2: Glutamate Emotion Memory Study Methods

This chapter provides an overview of the full study design and the specific design relevant to this thesis. This includes participant eligibility and recruitment, the intervention (including randomisation and blinding), and overall study procedures for the clinical study from which the data presented in Chapters 4-6 were collected. Detailed descriptions of questionnaire and task measures, computational modelling, and neuroimaging analyses are provided in the respective data chapters. This chapter therefore serves as a central overview of the study methodology, while chapter-specific procedures and analyses are described in those chapters.

Study Design

The study was conducted at the Department of Psychiatry, University of Oxford. This was a double-blind, placebo-controlled, randomised parallel-group study investigating the effects of ketamine on autobiographical memory, emotional processing, reward processing and decision-making in individuals with treatment-resistant depression (**Figure 3.1**). The DPhil thesis focused on the effects of reward processing **(Figure 3.2).**

The study consisted of five visits: screening, baseline assessment, infusion, scan one day post-infusion, and a follow-up approximately seven days post-infusion. These time points were selected to capture both the acute and early sustained effects of ketamine, which have been shown to emerge rapidly and peak within 24 hours following infusion and fade within 5-7 days. An overview of study is shown in **Figure 3.1**, and participant progression through the study is summarised in **Figure 3.3.**

Previous work has demonstrated large antidepressant effects of ketamine at 24 hours post-infusion (Hedges' g ≈ 1.2; Coyle & Laws, 2015). However, the neurocognitive outcome measures examined in the present study were novel, and the expected effect size for these measures was uncertain. Therefore, a conservative sample size calculation was conducted based on a moderate effect size (g = 0.7), indicating that 30 participants per group would provide 80% power to detect between-group differences.

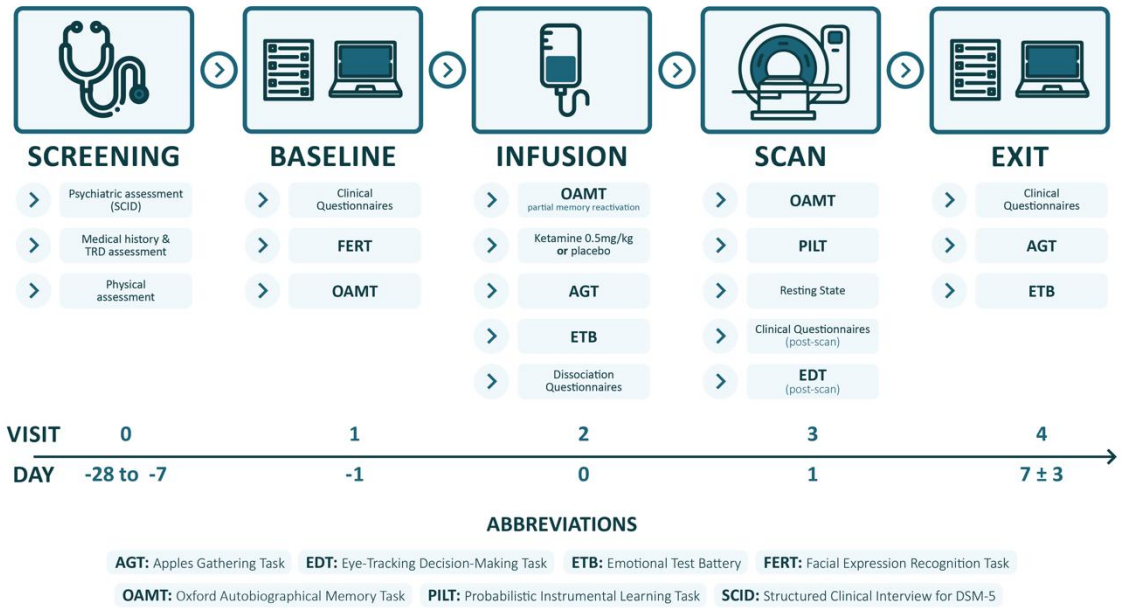


Figure 3.1. Overview of the GEMS study design.

Overview of the randomised, double-blind, placebo-controlled study investigating the effects of ketamine on autobiographical memory, emotional and reward-related processing in treatment-resistant depression. Participants completed screening, baseline assessment, ketamine or placebo infusion, post-infusion neurocognitive and neuroimaging assessments, and a follow-up visit. Multiple behavioural tasks and clinical questionnaires were administered across visits to assess emotional processing, reward learning, and clinical symptoms.

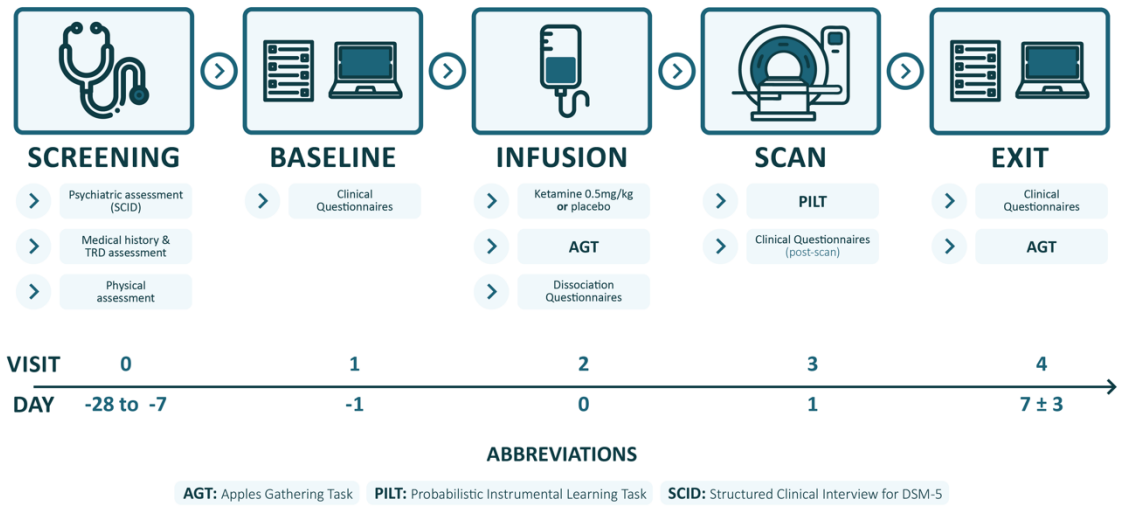


Figure 3.2. Thesis specific study design.

Overview of the study procedures and outcome measures analysed in the present thesis. Only behavioural and clinical measures relevant to reward processing and symptom change are presented, including the probabilistic instrumental learning task (PILT), Apples Gathering Task (AGT), clinical questionnaires, and follow-up assessments conducted 24 hours and approximately seven days post-infusion.

Participant Recruitment

Participants were recruited through advertisements in the local press, social media, and through collaboration with local health services and the TRD Clinic at the Warneford Hospital. Research advertisements were approved by the relevant Research Ethics Committee (REC) and disseminated via multiple platforms, including newspapers, websites, and social media. Additional recruitment occurred via referrals from clinicians in local clinics. All advertisements included details about the study and eligibility criteria.

Participant Eligibility

Participants had a current diagnosis of major depressive disorder, were currently in a major depressive episode of no longer than two years, were on an antidepressant for at least four weeks

and had shown no improvement. Participants had shown an inadequate response to one and no more than three antidepressant treatments at an adequate dose and duration. All participants were required to be fluent in English, capable of understanding the tasks, and provide informed consent.

Premenopausal women and male participants engaging in sexual activity with a risk of pregnancy were required to use effective contraception during the study. Participants were required to be in good physical health with no unstable medical problems, as determined by medical history, physical examination, electrocardiogram and blood and urine lab tests (including full blood count, liver, thyroid, and kidney function tests, toxicology screening, and pregnancy testing, for premenopausal women).

All participants completed MRI safety screening and were confirmed to be MRI-safe prior to participation. Additional eligibility requirements included registration with a GP and consent for their GP to be informed of study participation. Participants were required to abstain from alcohol for three days prior to the infusion visit and for one day prior to other study visits. Additional inclusion/exclusion criteria are outlined below:

Inclusion Criteria

- Age 20-60 years
- Current diagnosis of Major Depressive Disorder with inadequate response to one to three antidepressant treatments, as determined by the Structured Clinical Interview for DSM-5 (SCID-5)
- Fluent in English and able to complete cognitive tasks
- Consent to share medical information with GP
- Willingness to follow study protocols, including abstaining from alcohol and refraining from operating machinery post-infusion.

Exclusion Criteria

- History of bipolar disorder, schizophrenia, or substance use disorder
- Significant cognitive impairment or suicide risk
- Pregnancy, breastfeeding, or plans to conceive
- Contraindications to MRI or ketamine use
- Inability to comply with study procedures, including contraception requirements.

Participant Summary

Out of the 495 participants pre-screened, 352 were excluded for not meeting criteria, 143 pass pre-screening and attended a formal screening visit. Of these, 79 participants did not meet inclusion criteria, 57 declined to participants or extended for other reasons (**Figure 3.3**). Thus, 64 were enrolled and randomised, although 4 participants did not receive full allocation (**Figure 3.3**). A total of 28 participants were assigned to the ketamine group and 32 to the placebo group.

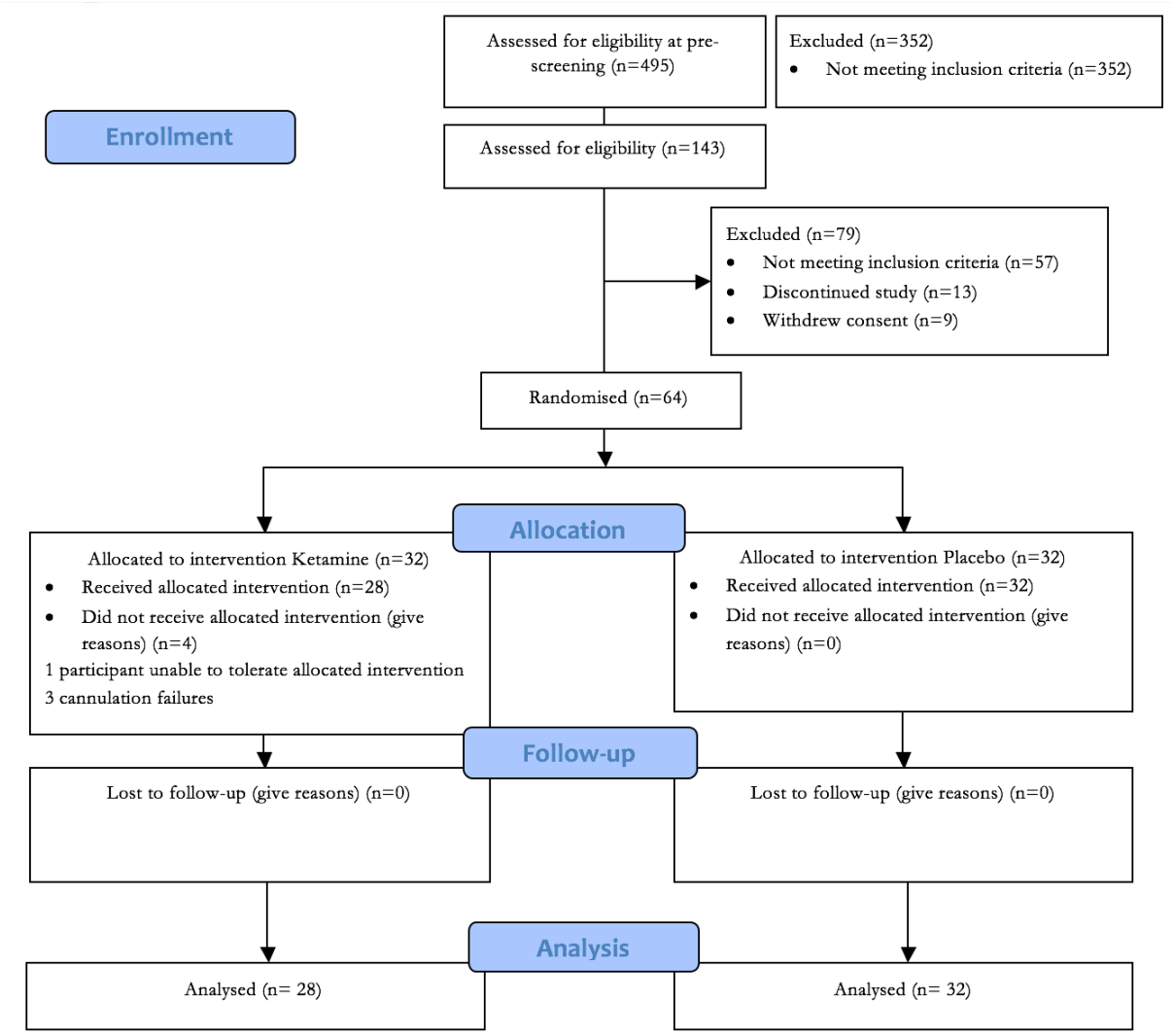


Figure 3.3 Participant flow through the study. CONSORT diagram showing participant screening, randomisation, dosing and follow up. Of the 495 individuals pre-screened, 64 met inclusion criteria and were randomised (ketamine, n=32; placebo, n=32). There is missing data for some of the task and questionnaires throughout the thesis, which will be explained in detail in the data chapters.

Randomisation and Blinding

Eligible participants were randomly assigned to receive either ketamine or placebo using an online randomisation tool (www.sealedenvelope.com). Randomisation was stratified by gender and task order. Both participants and direct research staff were blinded to treatment allocation, with

unblinding only occurring in the event of a medical emergency. The randomisation list containing the participant study ID and the allocation was updated when each new participant entered the randomised phase. The list was maintained by the Clinical Research Facility (CRF) at the Warneford Hospital.

Once a participant had provided informed consent and had been deemed eligible, they were assigned a unique study ID in sequential order. Medical staff responsible for administering the infusion accessed the pre-generated randomisation allocation immediately prior to infusion and administered the study drug accordingly. The randomisation process was documented, including the participant's study ID, treatment allocation, and the date and time of administration. This information was recorded on the randomisation code sheet and securely stored by the NIHR Oxford cognitive health Clinical Research Facility (CRF), Oxford Health NHS Foundation Trust at the Warneford Hospital.

Both participants and researchers conducting the 24-hour and 1-week follow-up visits remained blinded to treatment allocation. Only healthcare staff directly involved in the preparation and administration of ketamine or saline were aware of the treatment allocation.

A code-breaking protocol was in place for the duration of the study. The randomisation code was broken only in cases where it was necessary to know the participant's treatment allocation due to the emergence of a new medical condition or a serious adverse event. In such cases, the study pharmacy at Oxford Health NHS could be contacted by the research team using a 24-hour emergency contact number provided to participants at the baseline visit. If unblinding occurred, only the individual participant's treatment allocation was disclosed.

Ethics and Approval

The study received ethical approval from the NHS Research Ethics Committee (NHS REC; IRAS Project ID: 302265). The study was also registered on ClinicalTrials.gov (NCT05809609). All

participants provided written informed consent before participation. Participant safety was prioritised throughout the study. During ketamine administration, participants were monitored for potential adverse effects by medically trained staff, with continuous assessment of vital signs in line with the study protocol. Emergency medical support was available on site throughout the infusion and post-infusion monitoring period. Any adverse events were documented and managed in accordance with approved clinical and research governance procedures.

Participant confidentiality was maintained throughout the study. All data were anonymised using unique study identification numbers, and identifying information was stored separately from research data. Electronic data were stored on secure, password-protected servers, and paper records were kept in locked cabinets within restricted-access research facilities.

Interventions

Description of Intervention: Ketamine Hydrochloride at the dosage of 0.5 mg/kg. Ketamine is an approved anaesthetic agent that exerts a high-affinity non-competitive blockade of the glutamate N-methyl-d-aspartate (NMDA) receptor (NMDAR).

Control/Placebo: Saline solution of Sodium chloride 0.9% was used as inactive placebo. 43 mL of 0.9% saline was administered over 40 minutes using an infusion pump able to administer drugs at ml/hr connected via a tube extension to a peripheral indwelling venous cannula.

Administration Protocol: The drug was provided by the study pharmacy at Oxford Health NHS in ampoules for injection. The study drug was diluted in 43ml of 0.9% saline and administered over 40 minutes using an infusion pump able to administer drugs at ml/hr c connected via a tube extension to a peripheral indwelling venous cannula (43ml is used to account for residual volume in tubing between syringe and vein). The study medication was stored in a controlled drug cabinet in the CRF, accessible only to staff. It was stored between 20° to 25°C and protected by light. The

study drug was accounted using an agreed study documentation. Placebo was stored in a drug cabinet in the CRF, accessible only to staff. It was stored at 15-25 °C temperature and accounted for using agreed study documentation.

Concomitant Treatments: Participants were asked to stay on their current antidepressant at the same dose.

Study Visits Procedures

This section describes the study screening procedures and research visits. Only the procedures and measures for the tasks and questionnaires included in this DPhil thesis are described below.

Pre-screening

Participants who expressed an interest through our approved recruitment channels were sent a link to a Qualtrics survey form via email, which was a quick pre-screening form to filter out the key inclusion and exclusion criteria. Those who passed the quick pre-screening were directed to Calendly to book a telephone appointment with one of the researchers. The next stage was a telephone pre-screening.

The telephone pre-screening covered a more detailed list of key inclusion and exclusion criteria such as MRI contradictions, antidepressant past and current, history of recreational use, psychiatric disorder past and current, checking that participant could commit to this study. This lasted approximately 20-25 minutes. If the telephone screening outcome was a pass, the participant was booked in for a screening visit.

Screening Visit

Participants were asked about their psychiatric and medical history, and comprehensive clinical laboratory tests were performed, including full blood count, liver, thyroid, and kidney function tests, and urine analysis. Toxicology screening and pregnancy testing (for premenopausal women)

were also performed. Re-check of the MRI screening. Participants who met eligibility were invited to attend a baseline visit within four weeks of screening.

Baseline visit (Research Visit One)

At the baseline visit, participants completed self-report and clinician-administered questionnaires assessing depression (Quick Inventory of Depressive Symptomatology - Self-report; QIDS-SR; Hamilton Depressive Scale; HAM-D-17), anxiety (Generalised Anxiety Disorder-7; GAD-7), ruminative thinking (Ruminative Responses Scale; RRS), anhedonia (Temporal Experience of Pleasure; TEPS) and apathy (Apathy Motivation Index; AMI).

Following completion of the baseline visit, participants were scheduled to return for the infusion within one week.

Infusion Visit (Research Visit Two)

The infusion visit took place within one week of the baseline visit at the CRF at the Warneford Hospital. Upon arrival, inclusion and exclusion criteria were reviewed to confirm continued eligibility. Concomitant medications were reviewed, and any new medication taken since the baseline visit was recorded. Pregnancy testing and urine drug screening for illicit substances were conducted to ensure participant safety and minimise potential interference with study procedures.

Baseline physiological measurements, including blood pressure and heart rate were recorded, and participants were assessed for any new symptoms or adverse events. Baseline questionnaires were administered to assess dissociative symptoms (Clinician-Administered Dissociative States Scale; CADSS) and delusion ideation (Peters et al. Delusion Inventory; PDI).

Participants received either ketamine or placebo intravenously under medical supervision. The infusion lasted approximately 40 minutes. Post-infusion dissociative symptoms and delusional

ideation (CADSS and PDI) were reassessed, followed by the Apples Gathering Task (see Task Measures section).

Participants were monitored for 2-3 hours for vital signs and any adverse effects. Blood pressure was monitored every 10 minutes during the infusion and every 15 minutes for the hour following infusion completion.

Prior to discharge, participants completed a readiness to leave checklist to ensure it was safe for them to leave the facility. Participants were instructed to refrain from driving, cycling, or operating heavy machinery until they had slept or until the following morning, whichever occurred later.

Assessment Visit (Research Visit Three)

The assessment visit took place 24 hours after the ketamine/placebo infusion. Participants completed questionnaires assessing depression (HAM-D-17 and QIDS-SR), anxiety (GAD-7), rumination scores (RRS) and anhedonia (TEPS).

Participant were taken to OHBA for the scan part of the visit. Prior to scanning, participants completed MRI safety screening and changed into scrubs. Participants performed practice trials of the PILT before entering the scan. Participants were fitted with standard MRI equipment, including ear protection and a respiratory belt. A button box was provided to record task responses during scanning. Participant engagement and wakefulness were monitored throughout using the scanner eye-monitoring camera.

The MRI scan included a structural (anatomical) scan, and a probabilistic instrumental learning task (task-based fMRI). The total scan duration was approximately 90 minutes.

Exit Visit (Research Visit Four)

The exit visit occurred seven days after infusion (± 3-day). This time point was selected based on evidence that ketamine's antidepressant effects may begin to fade around 5 days post-infusion.

Participants completed questionnaires including measures of depression (HAM-D-17 and QIDS-SR), rumination (RRS), anhedonia (TEPS) and apathy (AMI). After questionnaires, participants completed the Apples Gathering Task (AGT).

At the end of the visit, participants were asked to guess their treatment allocation (ketamine or placebo) and to rate their confidence in this guess. Participants were subsequently debriefed, reimbursement was arranged, and information regarding an optional follow-up medical call about ketamine treatment was provided.

Measures

Questionnaires

Questionnaires were used to assess depression, anhedonia, apathy rumination and dissociation and delusions at different time points as mentioned above. Questionnaires were self-reported with the exception of the Hamilton Depression Rating Scale and Clinical Administered Dissociative States Scale (CADSS) which were administered by a trained researcher. These measures are reported in more detail in Chapter 4.

Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR16)

QIDS-SR was used to assess depressive symptoms at baseline, one day post infusion and 7 days post infusion. More information is provided in Chapter 4.

Hamilton Depression Rating Scale (HAM-D-17)

The HAM-D-17 is a clinician reported scale that was used to assess depressive symptoms at baseline, one day post infusion and 7 days post infusion. More information is provided in Chapter 4.

Temporal Experience of Pleasure Scale (TEPS)

The TEPS was used to assess pleasure which measures anticipatory and consummatory components of hedonic experience. This measure was administered at baseline, one day post infusion and 7 days post-infusion

Apathy Motivation Index (AMI)

Motivational impairments were assessed using the Apathy Motivation Index (AMI), a multidimensional self-report measure assessing behavioural activation, emotional sensitivity, and social motivation. This measure was administered at two time points, baseline and at 7 days post-infusion to coincide when the Apples Gathering Task was administered.

Hamilton Depression Rating Scale (HAM-D-17) – Libido

Sexual reward and libido were assessed using the sexual impairment item from the Hamilton Depression Rating Scale (HAM-D-17). This item provides a clinician-rated measure of sexual interest and functioning and was analysed to characterise changes in domain-specific reward function. This measure was administered at baseline, one day post infusion and 7 days post-infusion

Ruminative Response Scale (RRS)

Rumination was assessed using the Ruminative Response Scale (RRS), a self-report measure assessing repetitive negative thinking and maladaptive cognitive processing associated with

depression. This measure was administered at baseline, one day post infusion and 7 days post-infusion

Clinician-Administered Dissociative States Scale (CADSS)

Acute dissociative effects were assessed using the CADSS. This measure was collected pre-and post-infusion to confirm expected acute pharmacological effects of ketamine.

Peters Delusions Inventory (PDI)

Acute psychotomimetic effects were assessed using the PDI. This measure was collected pre-and post-infusion to confirm expected acute pharmacological effects of ketamine.

Cognitive Tasks

Probabilistic Instrumental Learning Task (PILT)

The PILT was administered 24 hours post-infusion inside the MRI scanner. This version of the task differed from that used in Study 1 (Chapter 2) in terms of outcome contingencies and was adapted for use during fMRI acquisition.

The PILT is a reinforcement learning task designed to assess reward-based decision-making that was adapted from the Pessiglione task (Halahakoon et al., 2024; Pessiglione et al., 2006). Participants were instructed that the goal of the task was to win as much money as possible by learning which abstract symbols were associated with a higher probability of winning money and which symbols were associated with a higher probability of avoiding a loss. On each trial, two abstract symbols were presented on the screen. Each symbol was probabilistically associated with an outcome. One symbol was associated with a high probability (0.7) of an optimal outcome (winning money on win trials or avoiding a loss on loss trials) and a low probability (0.3) of the opposite outcome (no win or loss, respectively). The other symbol had reciprocal contingencies. Participants selected one symbol on each trial and received feedback indicating the outcome of

their choice. The task consisted of 2 runs of 60 trials each and lasted approximately 15 minutes each run. More information about the task is provided in Chapter 5. A schematic of the task and trial structure is shown in **Figure 3.4**.

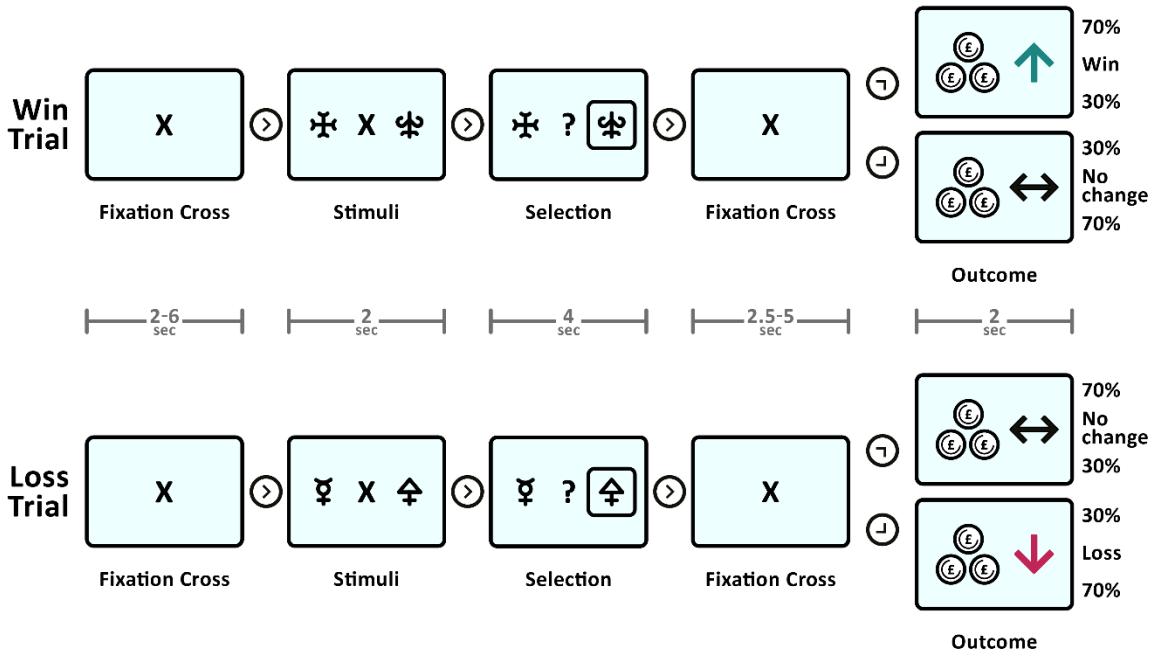


Figure 3.4 Schematic of the Probabilistic Instrumental Learning Task (PILT). Schematic of the win and loss trial structure, including jittered fixation intervals and probabilistic outcomes (70/30), used during the fMRI session.

Apples Gathering Task (AGT)

The AGT was completed twice during this study: 30 minutes after the infusion and 7 days after the infusion. The task was used to assess motivation to exert physical effort for rewards (Bonnelle et al., 2016; Bonnelle et al., 2015). The task was split into two phases: The Offers Phase **(Figure 3.5)** and Work Phase **(Figure 3.6)**, and lasted approximately 25 minutes. Further details on the task are provided in Chapter 6.

Offer Phase

On each trial participants were presented with a reward-effort combination offer. Participants decided if they wanted to accept or reject the offer based on the number of points (apples) and effort level (grip force). Participants were free to accept and reject as many offers as possible.

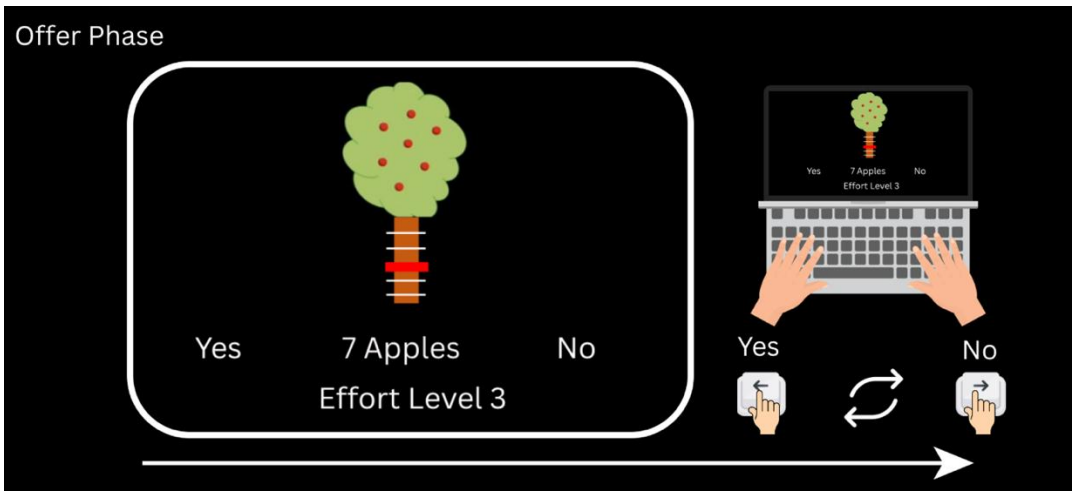


Figure 3.5 Example trial from the offer phase of the Apples Gathering Task (AGT).

Work Phase

The work phase consisted of 10 random offers that could be a mix of either accepted or rejected. Accepted offers required participants to exert physical effort to obtain the reward, whereas rejected offers required no action.

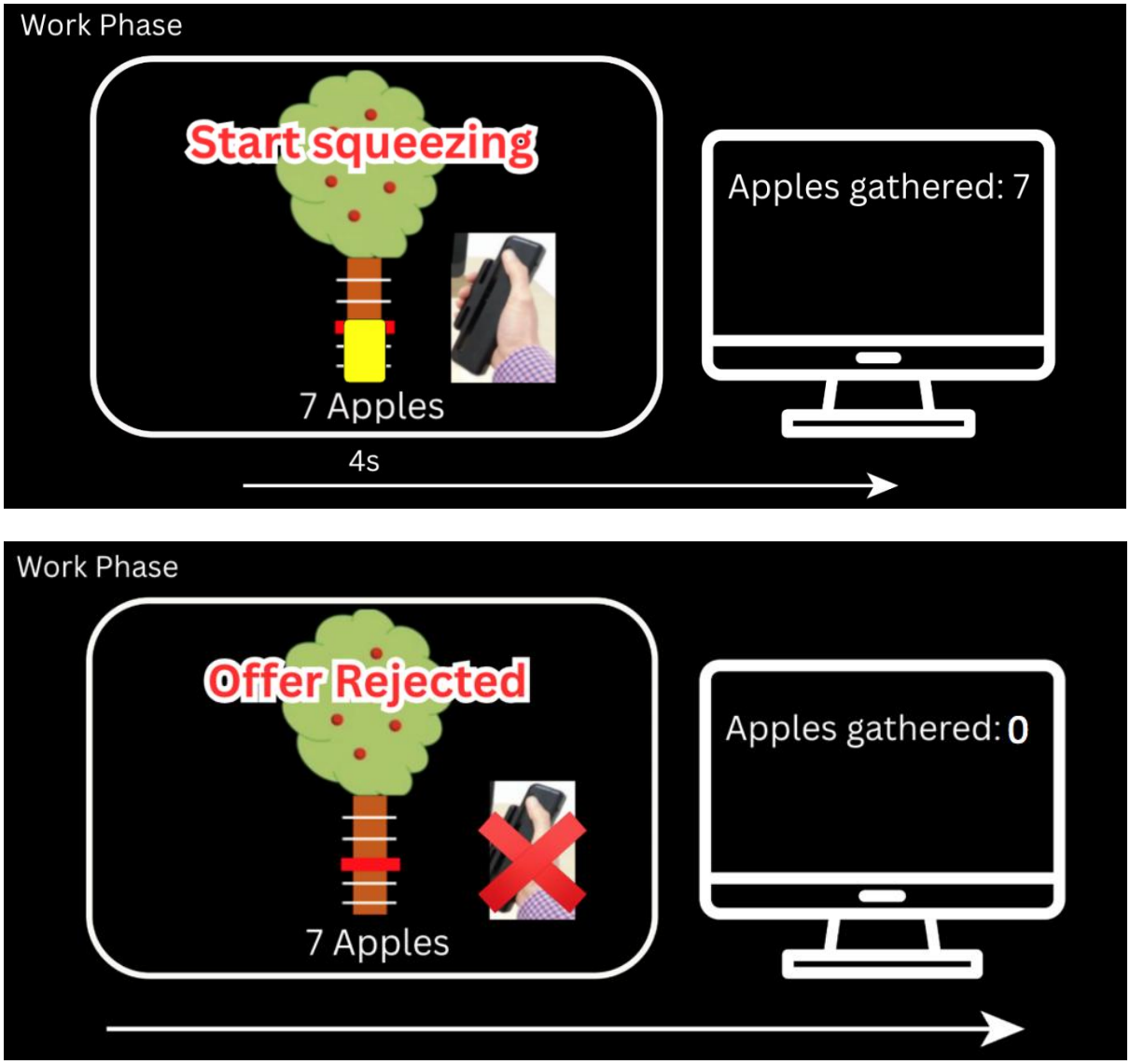


Figure 3.6 Example trial from the work phase of the Apples Gathering Task (AGT).

Statistical Analyses

PILT

Full details of task administration, pre-processing, statistical model specification and computational modelling are provided in the neuroimaging Chapter 5.

Accuracy data were analysed using mixed ANOVAs. To assess overall performance, accuracy across all trials was entered into a mixed ANOVA with Group (ketamine, placebo) as a between-subjects factor and Condition (reward, loss) as a within-subjects factor.

Reinforcement learning model specification and parameter estimation procedures are described in Chapter 5. Model parameters were estimated separately for each participant and separately for reward and loss trials. Learning rate (α) and inverse temperature (β) parameters were used as indices of learning dynamics and decision determinacy, respectively, and were compared between groups as specified in the Results.

AGT

Full details of task administration, pre-processing, and statistical model specification are provided in the AGT Chapter 6.

Analyses focused on behaviour during the offer phase of the task. The primary outcome was offer acceptance (accept vs reject), with secondary analyses examining offer-phase reaction times (RTs).

Offer acceptance was analysed using generalised linear mixed-effects models with a logistic link function, including fixed effects of reward level, effort level, treatment group (ketamine vs placebo), and time point, with participant-level random intercepts. Models were fitted both across time points and separately at each time point. Offer-phase RTs were log-transformed and analysed using linear mixed-effects models with the same fixed-effects structure. Significant interactions involving reward, effort, group, or time point were explored using simple-slope estimates of reward and effort sensitivity derived from marginal trends.

Neuroimaging

fMRI pre-processing and analysis

MRI acquisition parameters, pre-processing, registration, and full analysis procedures are described in Chapter 5. Briefly, pre-processing and statistical analyses were conducted using FSL (FMRIB Software Library). First-level analyses were implemented in FEAT using a general linear model (GLM) with explanatory variables representing task events and motion parameters included as nuisance regressors. Task regressors were convolved with a canonical haemodynamic response function.

For the PILT task, explanatory variables were specified to model anticipation and outcome phases of win and loss trials. First-level contrast images were generated for each participant and combined across runs using fixed-effects analyses to produce participant-level estimates.

Group-level analyses were conducted using FSL Randomise with 5000 permutations and threshold-free cluster enhancement (TFCE), with family-wise error correction applied at $p < 0.05$. The group-level GLM examined overall task effects and between-group differences (ketamine vs placebo). Full details of explanatory variables, contrasts, and modelling procedures are provided in Chapter 5.

Model-based fMRI regressors

Model-based fMRI regressors were generated using trial-wise expected values and reward prediction errors (RPEs) derived from a reinforcement learning model. These were included as parametric modulators at outcome within a first-level general linear model, alongside condition-based explanatory variables and motion parameters as nuisance regressors. Contrast images were generated at the participant level and entered into second-level general linear models to examine within-group and between-group effects. Full details of the explanatory variables, computational modelling, and fMRI analysis procedures are provided in Chapter 5.

Region of Interest (ROI) Analysis

Region of interest (ROI) analyses focused on striatal and related structures implicated in reinforcement learning and reward and loss processing. Anatomical ROIs were defined using the Harvard–Oxford Structural Atlas. Five ROIs were specified: left and right nucleus accumbens (ventral striatum), left and right dorsal striatum (comprising the caudate nucleus and putamen), and the insula. All ROI masks were thresholded at 50% probability and binarised prior to analysis.

Whole-brain and ROI analyses were restricted to grey matter using a grey matter probability mask thresholded at 20% and binarised prior to analysis. Full details of ROI definition and implementation are provided in Chapter 5.

Chapter 4: The Effects of Ketamine on Subjective States and Questionnaires

Introduction

Ketamine is a rapid-acting antidepressant, particularly for individuals who do not experience meaningful improvement with conventional monoaminergic treatments. Its antidepressant effects can appear within hours and often peak within the first 24 hours following infusion (Riggs & Gould, 2021). This rapid timescale provides a unique opportunity to examine early changes in depressive symptoms and reward-related processes, and to determine which components of reward function are most sensitive to ketamine. Evidence suggests that ketamine produces rapid anti-anhedonic effects that can occur independently of overall depressive symptom improvement, indicating a specific impact on anhedonia (Lally et al., 2014, 2015). Similarly, repeated administration of ketamine and esketamine has been shown to improve symptoms of anhedonia in individuals with treatment-resistant depression (Delfino et al., 2021; McIntyre et al., 2020; Wilkowska et al., 2021; Zheng et al., 2022). Characterising these symptom changes is therefore important for understanding how ketamine modulates reward function and clinical symptoms, and for interpreting its effects on underlying neurocognitive processes.

Depression is associated with disturbances across multiple components of reward function. In addition to low mood, individuals with depression commonly show impairments in pleasure, reduced motivation, altered sexual interest, and increased rumination, all of which influence engagement with rewarding and loss outcomes. These features reflect disruptions in partially dissociable components of reward processing supported by overlapping but distinct neurocognitive systems. Examining these components separately provides greater mechanistic specificity than global measures of depressive severity do, and may clarify how ketamine modulates reward function.

Historically, research and treatment in major depressive disorder (MDD) have focused primarily on mood symptoms. However, anhedonia is a core feature of depression that often persists despite improvement in mood and is associated with poorer clinical outcomes, including greater illness severity, functional impairment, and increased suicidality (Ballard et al., 2017; Spijker et al., 2001; Vinckier et al., 2017; Wichers et al., 2010; Winer et al., 2016). A recent analysis identified that greater anhedonia is associated with persistent suicidal ideation (Bloomfield-Clagett et al., 2022). Anhedonia is closely related to other symptoms such as apathy, fatigue, and avolition (Lambert et al., 2018; Pelizza & Ferrari, 2009) and is increasingly conceptualised as a transdiagnostic construct across multiple psychiatric and neurological disorders (Husain & Roiser, 2018; Trøstheim et al., 2020). Understanding how ketamine modulates reward-related symptoms is therefore central to clarifying its therapeutic effects and underlying neurocognitive mechanisms.

This thesis primarily examines behavioural and neuroimaging measures of reward learning, valuation, and motivation. These approaches provide sensitive measures of underlying neurocognitive processes but do not directly assess clinical symptoms or subjective reward experience. Including clinical questionnaires allows neurocognitive findings to be interpreted within a clinically meaningful framework and enables assessment of whether behavioural and neural changes are accompanied by changes in depressive symptoms and reward-related function. Importantly, this study was not designed as a clinical trial to evaluate treatment efficacy. Rather, assessing symptom changes provides important clinical context for interpreting neurocognitive findings and situating them within the broader effects of ketamine.

To address this, this chapter examines four specific domains of subjective experience that reflect distinct components of reward function and may be differentially modulated by ketamine: pleasure, motivation, libido, and rumination. These domains capture different aspects of hedonic

experience, motivational drive, sexual reward, and reward-related cognitive processes that shape how individuals experience, respond to, and learn from rewarding outcomes. Examining these components separately allows subjective symptom changes to be interpreted with greater mechanistic specificity and provides an important bridge between neurocognitive measures and clinical experience.

Ketamine also produces acute dissociative and psychotomimetic effects during infusion, which typically resolve within one to two hours (Acevedo-Diaz et al., 2020). At sub-anaesthetic doses, these effects are transient and can be reliably measured using validated clinical scales such as the Clinician-Administered Dissociative States Scale (CADSS) and the Peters Delusions Inventory (PDI). Assessing these effects confirms expected pharmacological responses and provides additional context for interpreting symptom and behavioural changes.

One key component of reward dysfunction in depression is impaired hedonic experience. Research examining ketamine's effects on anhedonia has commonly used self-report measures such as the Snaith-Hamilton Pleasure Scale (SHAPS). Ketamine has been shown to produce early changes in reward-related neural responses, with detectable alterations in reward-processing brain regions as early as two hours after infusion, even when self-reported symptoms do not significantly change (Kotoula et al., 2022). In contrast, other work has reported that anhedonia can improve rapidly following ketamine, and that these changes can occur partly independently of overall depressive symptom severity (Lally et al., 2015). However, the SHAPS primarily assesses hedonic capacity and does not distinguish between anticipatory and consummatory components of pleasure.

Current models of reward processing distinguish between anticipatory pleasure, which reflects the expectation of future reward, and consummatory pleasure, which reflects the experience of reward in the moment. These components are supported by partially dissociable neurocognitive systems

and may be differentially affected in depression and by antidepressant treatment. The Temporal Experience of Pleasure Scale (TEPS) enables separate assessment of anticipatory and consummatory pleasure, allowing more precise characterisation of hedonic function and providing greater specificity in assessing ketamine's effects on distinct components of reward processing.

Hedonic experience represents only one component of reward function. Reward processing also depends on motivational mechanisms that support the initiation and maintenance of goal-directed behaviour. These components are closely related but partially dissociable, and impairments in motivation may persist even when hedonic experience is relatively preserved. Examining both hedonic and motivational aspects of reward therefore provides a more comprehensive characterisation of reward dysfunction and may clarify how ketamine modulates distinct components of reward processing.

Beyond pleasure, motivational impairments represent another central component of reward dysfunction in depression. Apathy is characterised by reduced motivation, diminished goal-directed behaviour, and decreased initiation of action, and reflects impairments in processes that support effort allocation and engagement with reward (Husain & Roiser, 2018). Although related to anhedonia, apathy represents a partially dissociable construct, and these symptoms are associated with overlapping but distinct neurocognitive and neurobiological mechanisms (Bonnelle et al., 2015; Husain & Roiser, 2018). The Apathy Motivation Index (AMI) is a validated self-report measure that assesses individual differences in behavioural activation, emotional sensitivity, and social motivation, providing a multidimensional assessment of motivational dysfunction (Ang et al., 2017). Including measures of both hedonic experience and motivation allows differentiation between impairments in reward sensitivity and impairments in the initiation and maintenance of goal-directed behaviour, which may be differentially affected by ketamine and linked to distinct neurocognitive processes.

Sexual reward and libido represent a domain-specific component of reward function that integrates hedonic and motivational processes. Sexual reward integrates hedonic experience, motivational drive, and physiological arousal, and engages neural systems involved in broader reward processing (Calabrò et al., 2019; Safron et al., 2007, 2017). Sexual dysfunction is highly prevalent in depression and is frequently exacerbated by conventional antidepressant treatments, particularly selective serotonin reuptake inhibitors (SSRIs), which are associated with reduced libido, impaired arousal, and diminished orgasmic function (Baldwin, 2001; Montejo-gonzàlez et al., 1997). These impairments can persist even when other depressive symptoms improve. Despite its clinical importance and close relationship to reward processing, libido is rarely examined in studies of treatment response or anhedonia. Assessing measures of libido therefore addresses an important gap and provides a more comprehensive assessment of reward-related symptoms.

In addition to reward-related symptoms, cognitive processes that influence reward processing also play an important role in depression. Cognitive processes such as rumination play a critical role in depression and influence engagement with reward. Rumination involves repetitive, negative, self-focused thinking and is associated with reduced positive affect, impaired reward learning, and decreased responsiveness to rewarding stimuli (Segerberg et al., 2024; Whitmer & Gotlib, 2013). Rumination may also influence how individuals anticipate reward, evaluate its potential value, and respond to outcomes. Emerging evidence suggests that ketamine may reduce rumination early in treatment (Lehmann et al., 2016; Vidal et al., 2020), potentially contributing to improvements in reward engagement. Assessing rumination alongside reward-related domains therefore provides insight into how cognitive processes that maintain depression may change following ketamine.

This chapter therefore examines whether ketamine is associated with early changes in depressive symptoms and reward-related symptom domains, including pleasure, motivation, libido, and rumination, during the first week following infusion. By characterising changes across these

domains, alongside acute pharmacological effects, this chapter provides clinically meaningful context for interpreting behavioural and neuroimaging findings and clarifies how ketamine modulates distinct components of reward function.

Aims and Hypotheses

The aim of this chapter was to investigate whether ketamine is associated with early changes in clinical symptoms in treatment-resistant depression during the first week following infusion (one day and seven days post-infusion), compared with placebo. Outcomes included overall depressive severity and four specific reward-related symptom domains.

The four domains relevant to reward function and anhedonia were examined: pleasure, motivation, libido, and rumination. These domains reflect distinct but related components of reward processing that may be differentially affected by ketamine and are not fully captured by global measures of depression severity.

An additional aim was to characterise acute dissociative symptoms following ketamine administration using validated clinical scales. This provided confirmation of expected pharmacological effects and additional clinical context for interpreting symptom changes.

Based on evidence that ketamine produces rapid antidepressant and anti-anhedonic effects, the following hypotheses were tested:

H1: Participants receiving ketamine will show greater reductions in depressive symptom severity over the week following infusion compared with participants receiving placebo.

H2: Participants receiving ketamine will show greater improvement in pleasure over the week following infusion compared with participants receiving placebo.

H3: Participants receiving ketamine will show greater improvement in motivation over the week following infusion compared with participants receiving placebo.

H4: Participants receiving ketamine will show changes in libido over the week following infusion compared with participants receiving placebo.

H5: Participants receiving ketamine will show greater reductions in rumination over the week following infusion compared with participants receiving placebo.

Study Design

A detailed description of GEMS recruitment, screening, and infusion procedures is provided in Chapter 3. Briefly, participants were adults with treatment-resistant depression (TRD) enrolled in a randomised, double-blind, placebo-controlled experimental medicine study. Participants received a single intravenous infusion of either ketamine (0.5mg/kg) or placebo (0.9mg/kg of saline), under double-blind conditions. Participant completed five study visits: screening, baseline, infusion, scan (24 hours post-infusion) and exit visit (7 days post-infusion). Full details of the infusion procedure and visit schedule are provided in Chapter 3 (Methods).

Participants

Sixty participants were included in this analysis. A detailed description of the recruited sample is provided in Chapter 3.

Methods

Measures

Questionnaires were used to assess depression, anhedonia, apathy rumination and dissociation and delusions at different time points (see below). Most measures were self-reported, with the exception of the Hamilton Depression Rating Scale and Clinical Administered Dissociative States Scale (CADSS), which were administered by a trained researcher.

Depressive symptom severity

Depressive symptoms were assessed using the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR16) and the clinician-rated Hamilton Depression Rating Scale (HAM-D-17).

Quick Inventory of Depressive Symptomatology (QIDS)

The QIDS-SR is a self-report measure that assesses the severity of depressive symptoms over the preceding week (Rush et al., 2003). It captures core depressive symptom domains including mood, sleep, appetite and weight, concentration, psychomotor changes and suicidal ideation. Total scores provide an index of overall depressive symptom severity. This measure was administered at baseline, one day post-infusion and seven days post-infusion.

Hamilton Depression Rating Scale (HAM-D-17)

The HAM-D-17 is a widely used clinician-administered depression scale for assessing depressive symptom severity (Hamilton, 1960). The scale assesses a range of symptoms and aspects of depression including sleep quality, mood, guilty feelings, suicidal ideation, insomnia, agitation and somatic symptoms. The scale has been validated in adult populations with MDD. Total scores were analysed to characterise overall depressive symptom severity and to provide clinical context for reward-related symptom changes. This measure was administered at baseline, one day post-infusion and seven days post-infusion.

Pleasure (hedonic experience)

Temporal Experience of Pleasure (TEPS)

Pleasure was assessed using the Temporal Experience of Pleasure Scale (TEPS). The TEPS is an 18-item self-report measure with two subscales that assesses anticipation and consummation of

pleasure in physical rewards (Gard et al., 2006). The scale provides total and subscale scores and is commonly used to measure anhedonia-related processes. Total, anticipatory, and consummatory subscale scores were analysed to characterise distinct aspects of hedonic function. Lower scores indicate greater anhedonia. The measure was administered at baseline, one day post-infusion and seven days post-infusion.

Motivation (apathy)

Apathy Motivation Index (AMI)

Motivational impairments were assessed using the Apathy Motivation Index (AMI). The AMI is an 18-item self-reported measure with behavioural activation, social motivation and emotional sensitivity subscales (Ang et al., 2017). Items are rated on a five-point Likert scale, and provide a total and two subscale scores. The AMI has been validated in both healthy and neurological populations. AMI is a useful measure when studying overlapping symptoms such as anhedonia (Klar et al., 2022). High AMI scores indicate higher apathy. This measure was administered at baseline and seven days post-infusion.

Libido (sexual reward)

Hamilton Depression Rating Scale (HAM-D-17)

Sexual reward and libido were assessed using the sexual impairment item from the Hamilton Depression Rating Scale (HAM-D-17). This item provides a clinician-rated measure of sexual interest and functioning and was analysed to characterise changes in domain-specific reward function. This measure was administered at baseline, one day post-infusion and seven days post-infusion.

Rumination

Ruminative Response Scale (RRS)

Rumination was assessed using the Ruminative Response Scale (RRS), a self-report measure assessing repetitive negative thinking and maladaptive cognitive processing associated with depression. The RRS is a 21-item self-report questionnaire that assesses rumination. It consists of two subscales: brooding and reflection (Treynor et al., 2003). It has been shown to assess rumination independent of overall depression severity. Items are rated on a four-point Likert scale, with higher scores indicating greater levels of rumination. This measure was administered at baseline, one day post-infusion and seven days post-infusion.

Acute dissociative effects

Clinician-administered dissociative States scale (CADSS)

The CADSS is a structured clinician-administered scale used to assess state dissociative symptoms (Bremner et al., 1998). Total scores reflect the severity of dissociative experiences. This measure was administered during the infusion visit only (pre- and post-infusion).

Acute psychotomimetic effects

Peters et al., Delusion Inventory (PDI)

PDI is a self-reported questionnaire designed to measure delusion-like beliefs in the general population (Peters et al., 1999). It measures distress, preoccupation and conviction. This measure was administered during the infusion visit only (pre- and post-infusion).

Procedure

Participants completed validated clinical questionnaires assessing depressive symptoms and reward-related domains of subjective experience, including pleasure, motivation, libido, and

rumination **(Figure 4.1)**. Self-reported measures were administered via the Qualtrics platform on a testing laptop. The HAM-D-17 and CADSS were administered by a trained researcher.

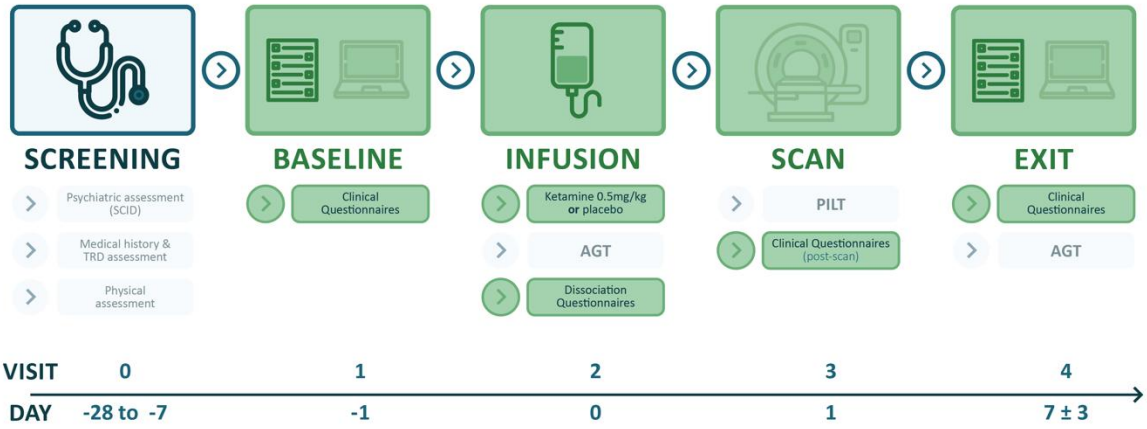


Figure 4.1. Figure of the study design. Participants completed questionnaires at all study visits highlighted in green, including assessments administered both before and after the infusion.

Data processing

All questionnaire data were extracted from Qualtrics website and processed using reproducible scripts written in R (version 4.3). Raw questionnaire exports were imported as CSV files and prepared for analysis. Data preparation included standardising variable names, removing non-data rows, and verifying consistency of item structure across time points.

Questionnaire responses were scored according to published scoring guidelines for each measure. Total scores and where applicable, subscale scores were computed with reverse scoring applied to relevant items prior to score calculation. Scoring procedures were applied consistently across participants and time points to ensure comparability.

Scored questionnaire datasets were merged across time points to create longitudinal datasets for analysis. Data were visually inspected using descriptive summaries and distribution plots to identify potential scoring errors, outliers, or data inconsistencies. Final processed datasets were saved as CSV files and used for all subsequent analyses.

Statistical Analysis

Questionnaire data were analysed using linear mixed-effects models in R. Each model included a random intercept for participant to account for repeated measures, and fixed effects of group (ketamine vs placebo), time point (baseline, 24 hours, 7 days), and their interaction.

The group x time point interaction was the primary effect of interest, as this test whether symptom changes differed between ketamine and placebo. Where significant interactions were observed, follow-up analyses were conducted to characterise the direction and timing of group differences.

Separate models were performed for:

- Depressive symptom severity (QIDS-SR16, HAM-D-17)
- Pleasure (TEPS total, anticipatory, consummatory)
- Motivation (AMI total and subscales)
- Libido (HAM-D-17 sexual impairment item)
- Rumination (RRS total)

Acute infusion-day effects

CADSS and PDI scores were analysed to assess acute dissociative effects of ketamine on the day of infusion. Pre-and post-infusion scores were analysed using linear mixed-effects models, including fixed effects of time point (pre, post), group (ketamine vs placebo) and their interactions, with random intercept for participants. The group x time point interaction tested whether acute

changes differed between ketamine and placebo. These analyses were conducted to confirm expected pharmacological effects and were considered descriptive and confirmatory rather than primary outcome analyses.

Results

This section outlines participant demographics, clinical characteristics **(Table 4.1)**, and response status **(Table 4.2)**.

Sociodemographic variables	**Ketamine (N=28)**	**Placebo (N=32)**
Age years - mean ± SD	29.71 (10.88)	32.34 (10.33)
Female, Male, Other, n (%)	18 (64%), 9 (32%), 1(0.04%)	21 (66%), 10(31%), 1(0.03%)
Years of education - mean ± SD	16.86 (2.21)	17.47 (3.31)
Ethnicity, n (%)		
White	24	24
Mixed/Multiple ethnic groups	2	1
Asian/Asian British	1	3
Black/African/Caribbean /Black British	1	-
Other ethnic group	-	1

Table 4.1 Demographics and clinical characteristics. Demographic information for all participants. *2 participant missing (2 placebo) for ethnicity and years of education. Categories are

based on the UK Office for National Statistics (ONS) 2021 classification. The "White" category includes participants identifying as English, Welsh, Scottish, Northern Irish or British, and those reporting any other White background (e.g., Polish, Russian, Portuguese, South African, European). The "Mixed/Multiple ethnic groups" category includes participants identifying with more than one ethnic background (e.g., White and Black African, White and Asian, or other mixed combinations).

Responder Status

Participants were classified as responders if they showed a ≥50% reduction in QIDS-SR16 score from baseline to Day 7. This classification was used for descriptive purposes only. Based on QIDS-SR16 scores, 19 participants (32%) met criteria for response (≥50% reduction from baseline to Day 7). Response rates were higher in the ketamine group (44%) compared with placebo (22%) **(Table 4.2)**.

Group	Responder (n, %)	Non-responder (n, %)
Ketamine (n=27)*	12 (44%)	15 (56%)
Placebo (n=32)	7 (22%)	25 (78%)
Total	19 (32%)	40 (68%)

Table 4.2. Clinical response classification based on ≥50% reduction in QIDS-SR16 score from baseline to day 7. *Response status could not be determined for one participant in the ketamine group due to missing exit visit data.

This section examines whether ketamine changed depressive symptoms and reward-related domains of subjective experience, including pleasure, motivation, libido, and rumination, during the first week following infusion.

Depression symptom severity

QIDS

There was a significant time x group interaction for QIDS scores, indicating that ketamine produced greater reduction in depressive symptoms over time compared to placebo [$F(2, 114) = 3.0$, $p = 0.05$; **Figure 4.2**]. Fixed effects tests showed that ketamine group reported significant reductions at 7 days, relative to baseline [$\beta = -2.82$, SE = 1.83, $t(114) = -2.38$, $p = .02$], whereas no significant changes was observed at the 24-hour scan visit when compared with the placebo group [$\beta = -1.97$, SE = 1.83, $t(114) = -1.67$, $p = 0.1$]. Change-score analyses confirmed significant baseline to exit improvement in the ketamine group [$t(56.31) = 2.36$, $p = 0.02$ (Ketamine: change mean = -8.2 Placebo: change mean = - 5.34].

Moderation by Baseline Depressive Severity

To examine whether baseline symptom severity moderated treatment response, baseline QIDS scores were included as a continuous moderator in the mixed-effects model. There was a significant baseline QIDS x time point interaction [$F(2, 110) = 5.92$, $p = <0.001$], indicating that individuals with higher depressive severity at baseline showed greater symptom change over time across both groups. However, the baseline QIDS x group x time point interaction was not significant [$F(2, 110) = 1.78$, $p = 0.2$]. This suggests that although higher baseline severity predicted larger overall improvements, it did not differentially influence the effect of ketamine relative to placebo. In other words, baseline depressive severity did not moderate ketamine's antidepressant effect.

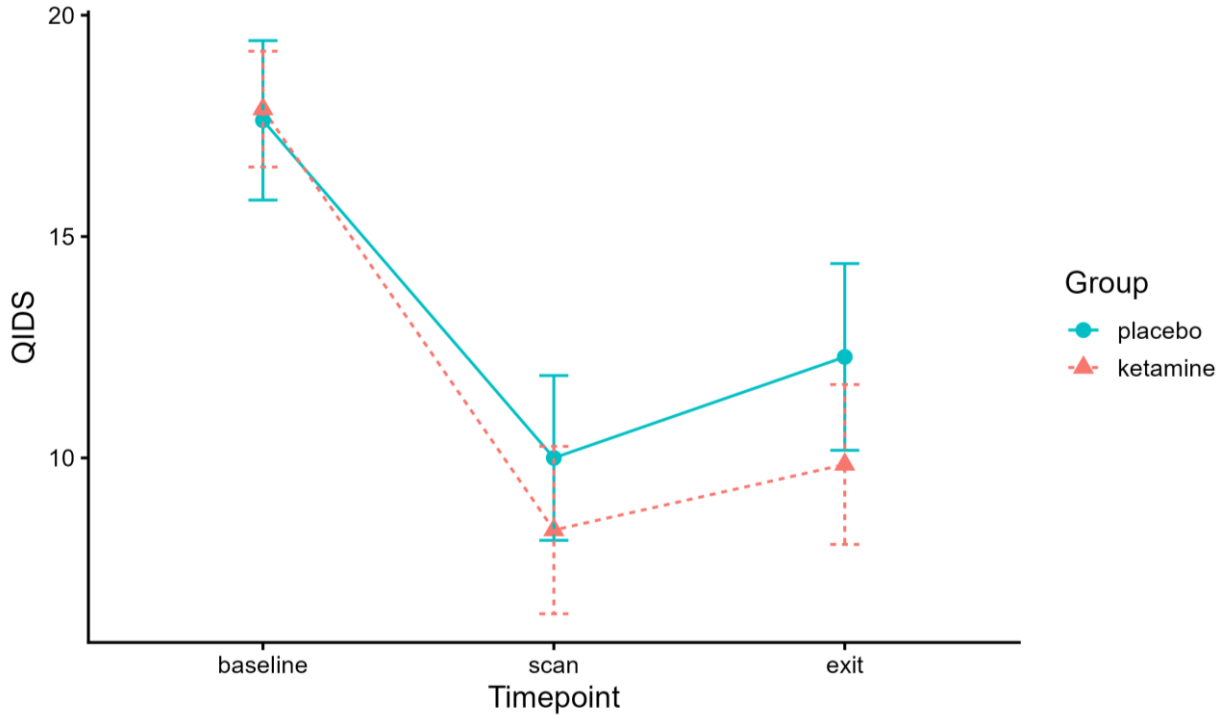


Figure 4.2. Mean QIDS scores over time in the ketamine and placebo groups. Error bars represent 95% confidence intervals.

HAM-D

There was a significant main effect of time [$F(1, 113) = 131.16$, $p < .001$] and main effect of group [$F(1, 58) = 3.98$, $p = 0.05$], indicating overall symptom reduction and significant differences between the groups. However, there was no significant time x group interaction [$F(2, 113) = 1.35$, $p = 0.26$], indicating that changes in HAM-D scores over time did not significantly differ between groups **(Figure 4.3)**.

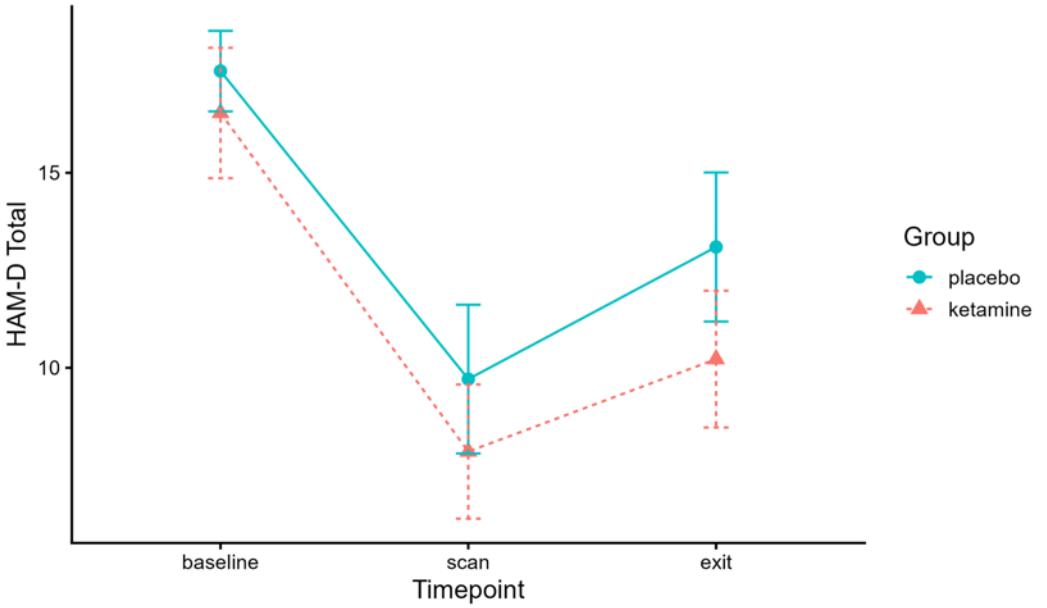


Figure 4.3. Mean HAM-D scores over time in the ketamine and placebo groups. Higher scores indicate greater depressive severity. Error bars represent 95% confidence intervals.

Pleasure

TEPS total

There was no significant main effect of time [$F(2, 114) = 1.40$, $p = 0.25$] nor group [$F(1, 58) = 0.45$, $p = 0.5$], or group x time interaction [$F(2, 114) = 0.24$, $p = 0.7$; **Figure 4.4**].

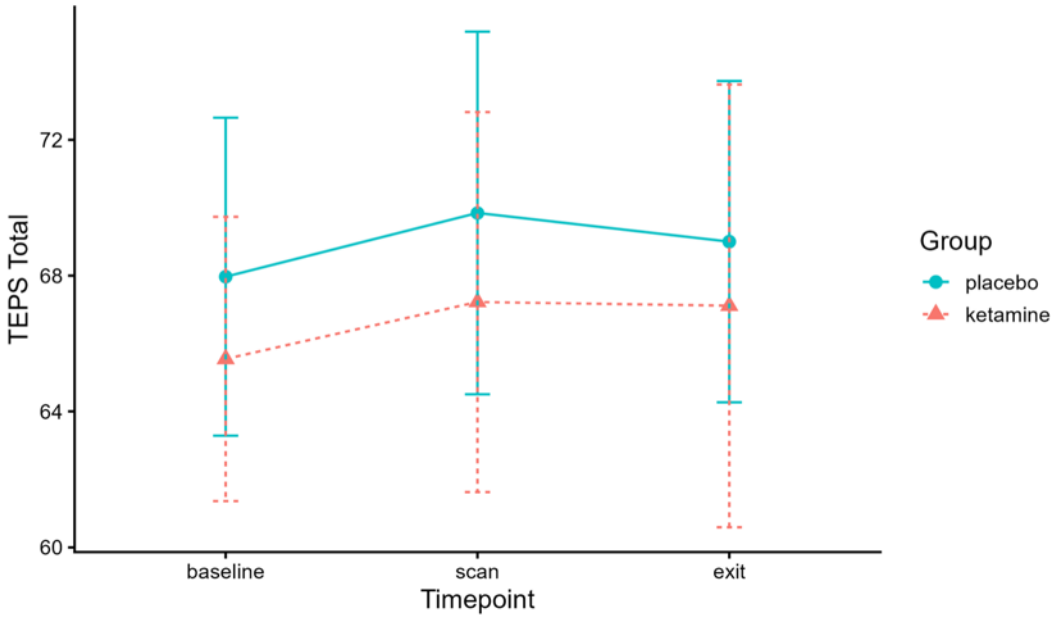


Figure 4.4. Mean TEPS total scores over time in the ketamine and placebo groups. Higher scores indicate greater pleasure capacity. Error bars represent 95% confidence intervals.

TEPS Consummatory

There was a significant main effect of time point [$F(2, 114) = 4.55, p = 0.01$] indicating that TEPS consummatory scores increased over time, reflecting improved consummatory pleasure across participants. There was no significant main effect of group [$F(1, 58) = 0.65, p = 0.42$] nor group x time interaction [$F(2, 114) = 0.48, p = 0.6$].

TEPS Anticipatory

There was no significant main effect of time [$F(2, 114) = 0.27, p = 0.76$] nor group [$F(1, 58) = 0.19$, p = 0.6], or group x time interaction [$F(2, 114) = 0.28, p = 0.7$].

Motivation

AMI Total

There was no significant main effect of time [$F(1, 57.55) = 3.26, p = 0.07$] or main effect of group [$F(1, 58) = 0.13, p = 0.7$] nor group x time interaction [$F(1, 57) = 0.26, p = 0.6$]. These findings indicate no significant improvements in apathy over time that were not specifically attributable to ketamine **(Figure 4.5)**.

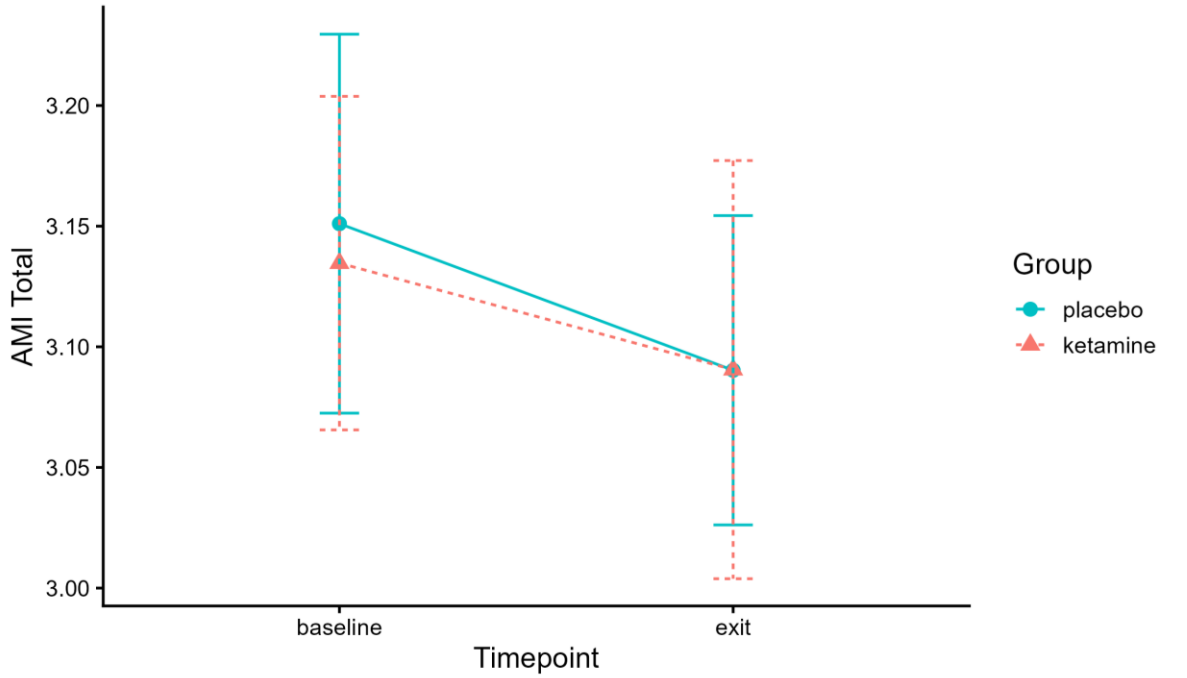


Figure 4.5. Mean AMI scores over time in the ketamine and placebo groups. Lower scores indicate lower apathy. Error bars represent 95% confidence intervals.

AMI Subscales

Apathy Motivation Index – Behavioural Activation

There was no significant main effect of time [$F(1, 57) = 0.58, p = 0.45$] nor group [$F(1, 57) = 0.31, p = 0.58$], or group x time interaction [$F(1, 57) = 0.47, p = 0.50$].

AMI Emotional Sensitivity

There was a significant main effect of time [$F(1, 57) = 14.49, p = <.01$], indicating that AMI scores decreased over time. nor group [$F(1, 58) = 0.82, p = 0.4$], or group x time interaction [$F(1, 57) = 0.08, p = 0.8$].

AMI social motivation

There was no significant main effect of time [$F(1, 57) = 3.26, p = 0.07$] nor group [$F(1, 58) = 1.41, p = 0.24$], or group x time interaction [$F(1, 57) = 0.22, p = 0.6$].

Libido (HAM-D Item 14)

There was a significant main effect of time [$F(1, 47)=14.27$, p <.001], indicating that scores decreased over time. There was no significant main effect of group [$F(1, 24) = 2.55$, $p = 0.1$] and no time x group interaction [$F(2, 47) = 0.38$, $p = 0.7$]. As shown in **Figure 4.6**, change over time did not significantly differ between the ketamine and placebo groups.

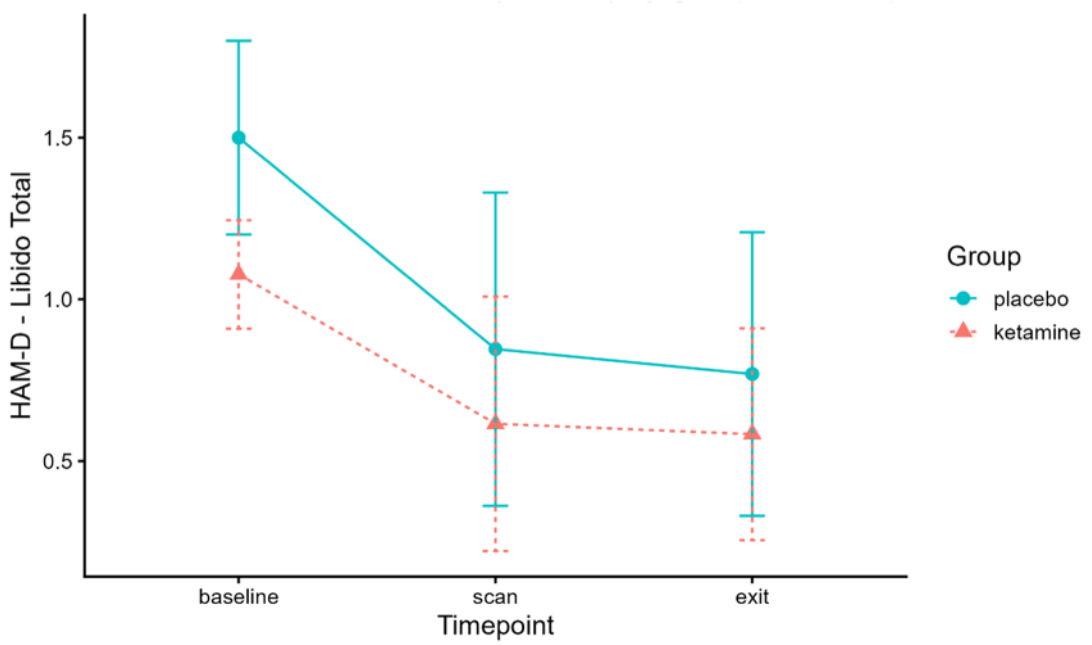


Figure 4.6. Mean Libido (HAM-D Item 14) scores over time in the ketamine and placebo groups. Higher scores indicate greater impairment. Error bars represent 95% confidence intervals.

Rumination

There was a significant main effect of time [$F(2, 114) = 36.77$, p <.001], indicating that rumination decreased over time across participants. There was also a significant main effect of group [$F(1,58) = 4.92$, $p = 0.03$], indicating that rumination scores were lower rumination scores overall in the ketamine group relative to the placebo group. The time point x group interaction was not significant, suggesting that both groups showed a similar pattern of reduction in rumination over time [$F(2, 114) = 1.74$, $p = 0.3$] **(Figure 4.7).**

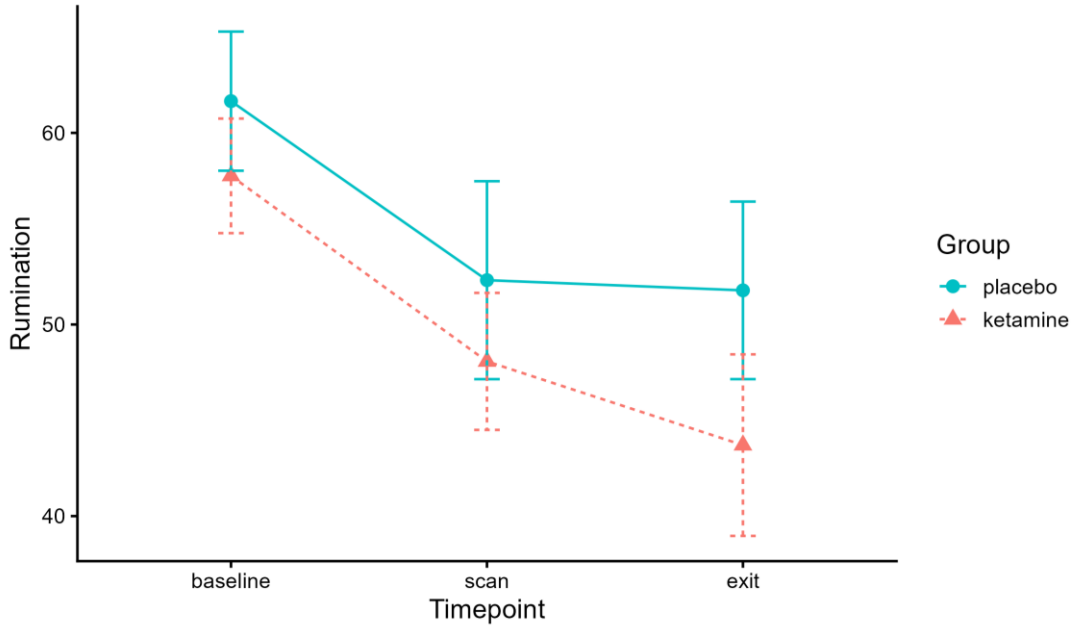


Figure 4.7 Mean rumination scores over time in the ketamine and placebo groups. Higher scores indicate greater rumination. Error bars represent 95% confidence intervals.

Acute infusion-day effects

Dissociative effects

Dissociative symptoms (CADSS)

CADSS scores differed significantly between groups over time, as reflected by a significant time x group interaction [$F(1, 59) = 62.32$, $p < 0.001$]. There was no significant difference in CADSS scores between groups pre-infusion ($p = 0.9$). However, CADSS scores were significantly higher in the ketamine group compared to the placebo group post-infusion **(Figure 4.8).** This indicates that dissociative symptoms were increased in the ketamine group relative to the placebo post-infusion.

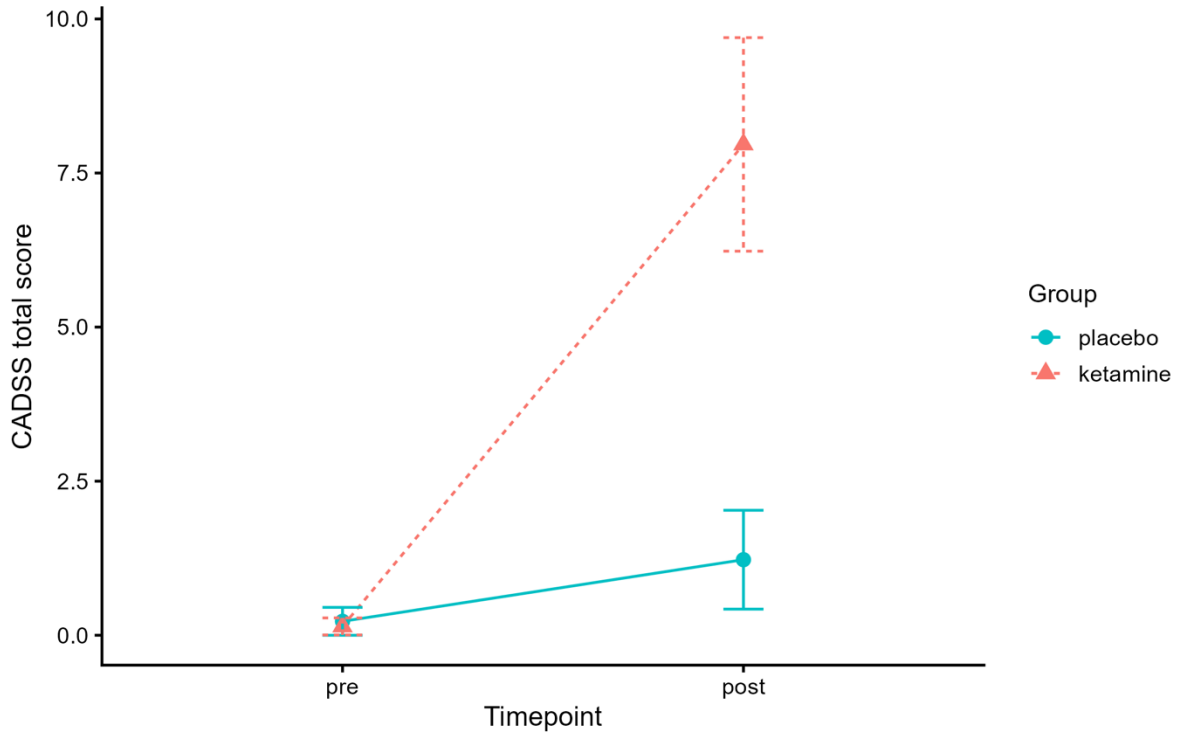


Figure 4.8. Mean Clinician-Administered Dissociative States Scale (CADSS) scores pre- and post-infusion in the ketamine and placebo groups. Higher scores indicate greater dissociative symptoms. Error bars represent 95% confidence intervals.

Dissociative symptoms (PDI)

In contrast, there was no significant main effect of time, group or time x group interaction for PDI scores [$F(1, 60) = 2.50$, $p = 0.1$]. The PDI scores increased slightly in the ketamine group from pre-infusion to post-infusion however, these changes did not differ significantly between groups **(Figure 4.9)**.

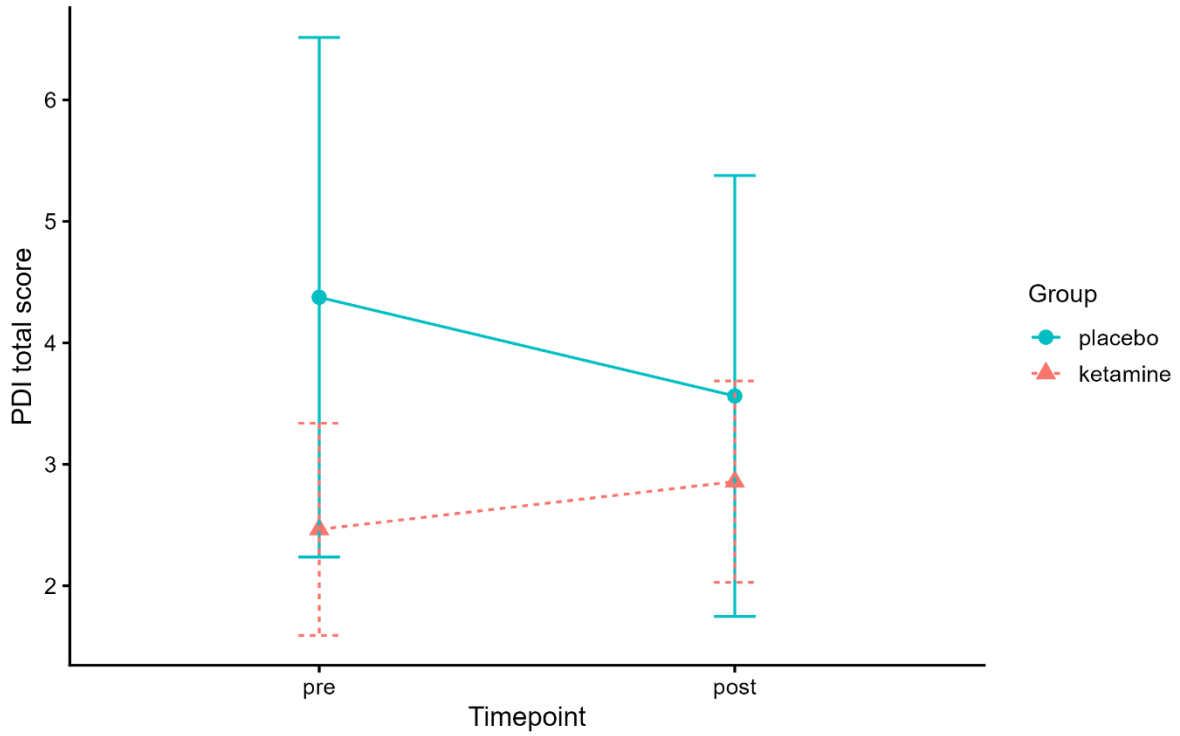


Figure 4.9. Mean Peters Delusion Inventory (PDI) scores pre- and post-infusion in the ketamine and placebo groups. Error bars represent 95% confidence intervals.

Discussion

This chapter examined whether ketamine produces early changes in depressive symptoms and reward-related domains of subjective experience, including pleasure, motivation, libido, and rumination, during the first week following a single infusion. Consistent with previous work, ketamine produced a modest reduction in depressive symptoms, reflected in a significant group x time interaction on the QIDS. In contrast, no significant group x time interaction was observed on the HAM-D, indicating that antidepressant effect was modest and not consistently detected across measures. Ketamine did not produce significant improvements in pleasure (TEPS), motivation (AMI), libido, or rumination relative to placebo, and the placebo group showed broadly similar improvements across several measures. This pattern may reflect a substantial placebo response, which is considered further in this discussion.

Effects on depressive symptoms

The observed QIDS group x time interaction is consistent with previous studies demonstrating rapid antidepressant effects of ketamine in TRD populations (Seshadri et al., 2024; Singh et al., 2016). Early improvements in depressive symptoms have been widely reported within 24 -72 hours following ketamine infusion, supporting its rapid therapeutic action.

In contrast, the HAM-D did not show a significant group-by-time interaction. Both groups showed marked reductions from baseline to 24 hours, followed by small increases at exit. One factor worth considering is the timeframe used for the HAM-D assessments. The baseline rating reflected symptoms over the preceding two weeks, whereas the post-infusion assessments covered much shorter periods. Some items, such as weight change, are unlikely to shift meaningfully over 24 hours, and mood symptoms can fluctuate across short intervals. As a result, the scale may not have been equally sensitive at each time point, which could have reduced the ability to detect treatment-specific differences. The QIDS may have been more responsive to early subjective changes, whereas the HAM-D focuses on clinician-rated observable symptoms.

Importantly, the overall antidepressant effect was modest, and the placebo group showed substantial improvement across several measures. This suggests that both pharmacological and non-specific treatment factors likely contributed to symptom change.

Effects of pleasure (TEPS)

Contrary to expectations and previous reports, ketamine did not produce significant improvements in hedonic experience as measured by the TEPS. This contrasts with studies reporting rapid anti-anhedonic effects following ketamine administration (Lally et al., 2014, 2015; Morris et al., 2020).

Although the TEPS has been widely used to differentiate anticipatory and consummatory components of reward processing, it was originally developed to assess relatively stable, trait-like aspects of pleasure experience. As such, it may be less sensitive to short-term state fluctuations following rapid-acting interventions, particularly when changes are subtle or nascent and not yet fully experienced.

Assessment timing may also be relevant. In the present study, TEPS was administered at 24 hours and 7 days post-infusion. If ketamine's effects on reward processing emerge earlier, or fluctuate within a narrower time window, it may not be reflected at these assessment points. For example, Morris et al. (2020) reported a significant difference in TEPS scores 40 minutes post-infusion. It is therefore possible that the combination of assessment timing and the trait-oriented structure of the TEPS reduced sensitivity to detect subtle between-group differences.

Sample characteristics may further contribute to the discrepancy. Baseline TEPS scores in Morris et al. (2020) were lower than those observed in the present sample, indicating greater baseline anhedonia. Greater baseline severity may provide greater capacity for measurable improvement, whereas higher baseline hedonic capacity may limit detectable change, particularly on a trait measure.

Finally, repeated ketamine administration may be required to produce measurable changes in self-reported hedonic function. Clinical studies have demonstrated greater improvements in reward-related symptoms following repeated dosing protocols (Wilkowska et al., 2021; Zheng et al., 2022), suggesting that early neurobiological changes may precede detectable subjective improvement.

These findings suggest that while ketamine produced modest improvements in overall depressive symptoms, its early effects on hedonic experience were not detectable using the TEPS at the assessment time points specified in this study.

Effects of motivation (AMI)

Ketamine did not produce significant changes in motivational impairments as measured by the AMI. Baseline AMI scores indicated substantial motivational impairment in this sample, consistent with previous work demonstrating high levels of apathy in TRD (Ang et al., 2017).

Motivational impairments may be more resistant to rapid pharmacological change than global depressive symptoms. Contemporary models distinguish between hedonic experience and motivational processes, which are supported by partially dissociable neural systems (Husain & Roiser, 2018). Ketamine's early antidepressant effects may therefore reflect improvements in mood or affective processing that do not immediately translate into measurable changes in goal-directed behaviour. It is also possible that repeated ketamine administration is required to produce clinically meaningful improvements in motivation, particularly in individuals with longstanding TRD.

Effects of libido

Ketamine did not produce significant improvements in sexual functioning as measured by the HAM-D sexual impairment item. This finding should be interpreted cautiously. Only a minority of participants exhibited sexual impairment at baseline, limiting statistical power to detect treatment effects. In addition, sexual functioning was assessed using a single clinician-rated item, which may lack sensitivity to detect subtle or early changes in sexual reward.

Sexual dysfunction in depression is strongly influenced by antidepressant medications (Kennedy & Rizvi, 2009; Montejo et al., 2015), which were continued during this study. These medications may have limited the extent to which ketamine-related changes in sexual reward could be detected. The absence of a significant effect therefore does not necessarily indicate that ketamine has no impact on sexual reward, but rather that the study may have been underpowered or that the measure was not sufficiently sensitivity to detect change.

It is a strength that the study considered sexual dysfunction, which is a clinically significant concern in depression, future studies should consider include a validated measure of sexual functioning. Measurements such as the Arizona Sexual Experiences Scale (ASEX; Elnazer & Baldwin, 2020) or the Changes of Sexual functioning Questionnaire (CSFQ; Clayton et al., 1997) may provide greater sensitivity than a single item from the HAM-D.

Effects of rumination

Ketamine did not produce significant reductions in rumination compared with placebo. Rumination is a cognitive process closely linked to reward processing, influencing how individuals anticipate and respond to rewarding outcomes (Segerberg et al., 2024; Whitmer & Gotlib, 2013). Although previous studies have reported early reductions in rumination following ketamine administration (Lehmann et al., 2016; Vidal et al., 2020), the present findings suggest that such effects may be smaller or more variable in medicated TRD populations.

It is possible that cognitive processes such as rumination require longer timeframes or repeated ketamine administration to show measurable change. Alternatively, reductions in rumination may emerge secondary to broader improvements in mood or reward processing rather than occurring immediately following treatment.

Acute dissociative effects

As expected, ketamine produced significant acute dissociative effects, reflected in increased CADSS scores during infusion. This confirms that participants experienced the expected pharmacological effects of ketamine. PDI scores also increased but did not differ significantly between groups, suggesting that ketamine's acute effects were primarily dissociative rather than increased delusional ideation. These findings confirm the pharmacological validity of the infusion and demonstrate that the absence of reward-related symptom change was not due to insufficient drug exposure.

Placebo effects

The improvement observed in the placebo group across several questionnaire outcomes is important to consider. Large placebo responses are well documented in depression trials, including studies of ketamine and esketamine, and are typically attributed to expectancy effects, therapeutic contact, structured follow-up, regression to the mean, and natural symptom fluctuation. In infusion-based designs, the treatment context itself may further enhance these non-specific effects (Matsingos et al., 2024).

In this study, placebo participants showed a broadly similar pattern of change to the ketamine group on most self-report measures, and many outcomes did not differ significantly between groups. The significant QIDS result in the ketamine group therefore likely reflects a modest drug effect occurring alongside non-specific improvement processes that influenced both groups. It is also important to note that all participants were taking an antidepressant during the study. The additional clinical and researcher contact, together with the expectation that the infusion might help them feel better, may have contributed to the symptom improvement observed in the placebo group.

These substantial placebo and contextual influences, combined with the TRD sample and reliance on self-report measures, may have reduced the ability to detect more subtle or more mechanistically specific ketamine effects on reward and motivation. This raises the possibility that early ketamine-induced changes in reward processing may initially occur at behavioural or neurocognitive levels before becoming fully accessible to subjective awareness, highlighting the importance of integrating behavioural and neuroimaging measures alongside self-report assessments.

Measurement consideration

Beyond measure-specific issues, broader methodological factors may also have limited sensitivity to detect early reward-related changes.

TEPS was used in this study due to its differentiation between anticipatory and consummatory pleasure; however, it may be less sensitive to short-term fluctuations or subtle early changes following a single infusion. State-sensitive measures such as the Snaith–Hamilton Pleasure Scale (SHAPS), which are more sensitive to short-term symptom change (Lally et al., 2014, 2015), may complement TEPS in future studies. Reduced sensitivity of the TEPS to acute changes has also been noted in previous work (Chan et al., 2012; Strauss et al., 2011). While the TEPS provides important mechanistic specificity by separating anticipatory and consummatory pleasure, it may require larger sample sizes or longer follow-up periods to detect small treatment effects.

More broadly, self-report questionnaires rely on subjective awareness and may not fully capture early changes in reward processing, particularly if such changes occur at neurocognitive or neurobiological levels before they become consciously accessible (Husain & Roiser, 2018;

Thomsen, 2015). In addition, strong placebo and contextual influences on subjective ratings may further reduce the ability to detect subtle drug-specific effects. The AMI, although focused on apathy and motivation, is also a self-report instrument and subject to similar limitations.

Concomitant antidepressants

Participants remained on their antidepressant medication during the study. This design reflects real-world clinical practice, where ketamine is often administered as an adjunct rather than as a standalone treatment. However, it is important to acknowledge that the effects of ketamine in medicated patients are less well understood. In particular, it is unclear whether reward-processing deficits in individuals already taking antidepressants may require multiple ketamine infusions before meaningful change is observed. Antidepressants can influence reward sensitivity, and this may have reduced the extent to which early ketamine-related improvements in anhedonia could be detected.

Strength and limitations

This study has several strengths. It used a placebo-controlled design and examined multiple reward-related domains, including pleasure, motivation, libido, and rumination, providing a comprehensive assessment of subjective reward function. Sexual reward was examined despite being underexplored in previous ketamine studies, addressing an important gap in the literature. The inclusion of a medicated TRD sample enhances ecological validity and clinical relevance.

Several limitations should also be acknowledged. The sample size may have limited statistical power to detect small treatment effects in specific reward domains. The use of a single ketamine infusion may have been insufficient to produce measurable changes in reward-related symptoms. Reliance on self-report measures may have reduced sensitivity to early neurocognitive changes.

Concomitant antidepressant use introduces potential confounding effects. Treatment-resistant depression is associated with more persistent and treatment-refractory reward-processing impairments, which may require longer treatment duration or repeated ketamine administration to show measurable improvement. The present findings therefore highlight the importance of considering illness chronicity and treatment resistance when interpreting ketamine's effects on reward-related symptoms.

Conclusion

In summary, ketamine produced modest antidepressant effects but did not produce detectable early improvements in pleasure, motivation, libido, or rumination in this medicated TRD sample. These findings suggest that global depressive symptoms may improve earlier than reward-related symptom domains, or that early changes in reward processing may not be fully captured by self-report measures. This pattern supports emerging models proposing that ketamine's early effects may primarily influence affective and neurocognitive processes, with downstream behavioural and subjective changes emerging over longer timeframes. These findings provide important clinical context for interpreting behavioural and neuroimaging results presented in subsequent chapters and contribute to understanding the domain-specific and temporal dynamics of ketamine's effects on depression.

Chapter 5: GEMS - The effects of Ketamine on reward processing using computational and neuroimaging methods

Introduction

Reward and loss processing deficits in depression

Neuroimaging studies have consistently reported blunted striatal response to rewarding outcomes, particularly within the ventral striatum (VS) in MDD. Reduced VS activation during reward receipt has been reported across a range of reward-processing tasks, suggesting reduced responsivity to positive outcomes in depression (Keren et al., 2018; Ng et al., 2019; Pizzagalli et al., 2009; Steele et al., 2007). Reduced activation has also been reported across other striatal subregions, including the nucleus accumbens, caudate, putamen during reward processing tasks, further supporting striatal dysfunction in reward-related deficits (Pizzagalli, 2014).

While many of the studies have focused on responses to rewarding outcomes, there is growing evidence that neural responses to losses are also altered, and that reward and loss processing may be differentially affected in depression (Admon & Pizzagalli, 2015). A meta-analysis specifically investigating loss processing in the monetary incentive delay (MID) task, which has two distinct stages (anticipation and outcome) found that loss anticipation was associated with activation in the anterior and mid-cingulate cortex, bilateral insula, and striatal regions including the nucleus accumbens, and caudate/putamen (Dugré et al., 2018). In contrast, loss outcome was associated with activation primarily in the bilateral putamen, right insula, and anterior cingulate cortex (Dugré et al., 2018). Together, these findings highlight the importance of examining both positive and negative outcomes when studying reward-related dysfunction in depression, rather than focusing exclusively on reward responses.

Although striatal abnormalities have been relatively consistently reported in depression, findings in prefrontal regions have been more heterogeneous. Several studies have reported increased activation in regions such as the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and middle frontal gyrus during reward processing in depressed individuals (Forbes et al., 2006; Keedwell et al., 2005; Mitterschiffthaler et al., 2003; Smoski et al., 2009) whereas other studies report reduced activation in similar prefrontal areas, including the frontal pole. These inconsistencies may relate to differences in task design, statistical power, outcome valence, or the specific stage of reward processing being studied. As a result, while fronto-striatal dysfunction is widely implicated in depression, the precise role and direction of prefrontal alterations in the context of reward and loss processing remains unresolved.

Importantly, reward processing can be split into multiple components as mentioned above. Studies have suggested that depression may be associated with altered neural responses at different stages of reward processing, with some studies reporting abnormalities during anticipation and others during outcome receipt (Forbes et al., 2009; Keren et al., 2018; Pizzagalli et al., 2009). However, other studies have failed to observe differences between depressed individuals and controls at either stage, further contributing to inconsistencies in the literature (Ng et al., 2019). Clarifying whether abnormalities are stage-specific in reward processing therefore remains an important unresolved question.

Reinforcement learning

While outcome-related activation provides important information about how people with depression respond to wins and losses, reward processing also depends on learning from feedback over time. Learning requires individuals to update expectations about future outcomes based on feedback and to adjust their behaviour in order to maximise positive outcomes and minimise

negative ones. Within computational neuroscience, these processes are commonly described using reinforcement learning frameworks in which feedback drives incremental updating of expected values through reward prediction errors (RPEs), defined as the difference between expected and received outcomes (Schultz, 2016). Reinforcement learning models are useful for examining how behaviour is shaped by feedback. RL models allow observable choices to be disentangled into latent computational parameters, such as learning rates and decision sensitivity which could play a role in neural and molecular processes involved in value updating and action selection (Lan & Browning, 2022).

Probabilistic instrumental learning tasks offer an experimental framework in which participants gradually learn the reward or loss probabilities associated with different actions through trial-and-error experience. Functional neuroimaging studies using such tasks have shown that model-derived RPEs correlate with BOLD responses in the striatum, with phasic increases observed for positive RPEs and decreases for negative RPEs (Daw & Tobler, 2014; Niv, 2009). RPE-related neural activation therefore provides a useful index of learning processes that may be impaired in depression. Importantly, these tasks allow outcome-related neural responses to win and losses to be modelled separately from learning-related signals. This approach provides a more precise investigation of whether deficits in depression are altered outcome, valuation, impaired learning from feedback or both.

Altered reinforcement learning mechanisms in depression

There is growing evidence that reinforcement learning mechanisms are altered in depression. Behavioural studies have reported reduced learning from positive outcomes and altered sensitivity to negative feedback, suggesting abnormalities in how expectations are updated based on experience (Chase et al., 2010; Chen et al., 2015; Chiu & Deldin, 2007; Huys et al., 2013; Pizzagalli

et al., 2009). Neuroimaging work has further shown attenuated RPE-related signals in depression, particularly within the ventral striatum, consistent with hypotheses of reduced dopaminergic signalling (Kumar et al., 2018). Reduced RPE signals have also been reported in regions such as the dorsal anterior cingulate cortex, striatum, thalamus, and midbrain, with reductions associated with anhedonic symptom severity in some studies (Chase et al., 2010). In contrast, other studies have reported increased sensitivity to negative or aversive outcomes, particularly in older adults with major depressive disorder (Dombrovski et al., 2013, 2015), suggesting that reward and loss learning may be differentially affected across individuals or clinical populations.

Supporting this point, a recent meta-analysis reported that partially distinct neural systems are involved in encoding prediction errors across reward and loss domains (Dugré et al., 2018). Reward-related prediction errors were associated primarily with activity in the striatum, frontal operculum, and midbrain, whereas aversive-domain prediction errors engaged regions including the insula, thalamus, and habenula (Dugré et al., 2018). Importantly, prediction error signals in aversive contexts may reflect broader processes such as salience or context-dependent updating during loss learning, rather than simple responses to negative outcomes. Nevertheless, findings across regions and studies remain heterogeneous, and the extent to which reward and loss learning are differentially affected in depression remains unclear.

Ketamine's role in depression, reward and learning

Ketamine is a non-competitive NMDA receptor antagonist that has been shown to exert rapid antidepressant effects, including reductions in anhedonia with these effects emerging within hours of administration and lasting for several days. Peak antidepressant responses have been reported approximately 24 hours after administration of a single subanaesthetic dose (typically 0.5 mg/kg) (Murrough et al., 2013; Zarate et al., 2006). Reductions in anhedonia following ketamine have also

been associated with increased glucose metabolism in regions such as the dorsal anterior cingulate cortex and hippocampus (Lally et al., 2015).

Neuroimaging studies further indicate that ketamine induces widespread changes in brain connectivity. In a global brain connectivity study in MDD, reduced connectivity was largely normalised 24 hours after ketamine with responders showing increased connectivity within prefrontal, striatal and insular regions (Abdallah et al., 2018). These findings suggest that ketamine engages neural systems implicated in affective and reward-related processing.

Task-based neuroimaging studies exploring ketamine's effects on reward processing have reported alterations in neural responses to feedback. For example, Morris et al. (2020) found that ketamine reduced sgACC hyperactivation to positive, but not negative, outcomes suggesting a valence-specific modulation of outcome related processing. However, the study did not report a significant effect of ketamine on activation during the anticipation phase. More recently, Kotoula et al. (2022) reported increased activation in striatal regions, including the nucleus accumbens and putamen during a monetary reward task two hours after ketamine administration in unmedicated individuals with remitted depression. In that study, ketamine effects were more prominent for win outcomes compared with neutral outcomes. However, the study did not include loss trials, making it unclear whether ketamine modulates neural responses to negative outcomes. In addition, the participants were individuals with remitted depression rather than those experiencing a current depressive episode, which may have affected the pattern of effects.

To date, no study has directly tested the effects of ketamine on neural response to reward and loss using computational modelling in individuals with treatment-resistant depression, a population characterised by persistent reward-processing deficits.

Study Aims and Rationale

The present study investigated the effects of ketamine on neural responses to wins and losses and on reinforcement learning mechanisms in individuals with treatment-resistant depression. The study used a probabilistic instrumental learning task combined with reinforcement learning modelling and functional neuroimaging one day following ketamine infusion.

The striatum, particularly the nucleus accumbens and dorsal striatum, plays a key role in reward valuation and reinforcement learning and was therefore a primary focus of the present study. However, reward and loss processing are supported by broader fronto-striatal networks, and ketamine has been shown to exert effects beyond core reward regions. To capture these broader effects, whole-brain analyses were conducted alongside striatal region-of-interest analyses.

The one-day post-infusion time point was chosen as this corresponds to the period at which ketamine's antidepressant effects are considered to be at or near their peak. This time window therefore provides an opportunity to investigate ketamine-related changes in neural activation associated with reward and loss processing.

Anhedonia and reward-related deficits are particularly prominent and persistent in treatment-resistant depression; therefore, this population was selected for the present study. Although there is evidence that ketamine exerts anti-anhedonic effects, it remains unclear how these effects relate to behavioural performance and neural responses during reward and loss processing in medicated individuals with treatment-resistant depression. Furthermore, much of the existing neuroimaging literature has focused primarily on neural responses to rewarding outcomes, with comparatively limited investigation of loss processing. Examining neural responses to both reward and loss, alongside computational indices of reinforcement learning, may therefore provide a more comprehensive account of ketamine's effects on affective and motivational processing.

Hypothesis

Hypothesis 1: Ketamine will be associated with altered neural responses to rewarding outcomes, reflected in increased activation within striatal regions during win outcome processing compared with placebo.

Hypothesis 2: Ketamine will be associated with attenuated neural responses to loss outcomes within striatal and salience-related regions, including the insula, compared with placebo.

Hypothesis 3: Ketamine-related changes in outcome-related neural activation will be accompanied by modulation of reinforcement learning signals, including prediction error-related responses within fronto-striatal and salience-related circuitry.

Hypothesis 4: Ketamine will be associated with differences in reward and loss learning behaviour, reflected in altered choice behaviour and/or reinforcement learning parameters during the probabilistic instrumental learning task compared with placebo.

Methods

Study Design

A detailed description of GEMS recruitment, screening, and infusion procedures is provided in Chapter 3. Briefly, participants were adults with treatment-resistant depression (TRD) enrolled in a randomised, double-blind, placebo-controlled experimental medicine study. Participants received a single intravenous infusion of either ketamine (0.5mg/kg) or placebo (0.9mg/kg of saline) administered over a 40-minute period, under double-blind conditions. Full details of the infusion procedure and study visit are provided in the method chapter (Chapter 3). The study was approved

by the NHS Research Ethics Committee (IRAS Project ID: 302265) and registered on ClinicalTrials.gov (NCT05809609). All participants provided written informed consent.

Participants

Of the 60 participants enrolled, 56 were included in the present analysis (ketamine n=27; placebo n=29). One participant was unable to attend the scan visit due to scanner-related technical issues, two were unable to complete the scan visit, and one was unable to attend due to COVID.

Questionnaires

Depressive symptoms and anhedonia were assessed using the HAM-D, TEPS and QIDS. Full measure descriptions, scoring procedures and administration time points across the broader study are provided in Chapter 4.

Probabilistic Instrumental Learning Task

Participants completed fMRI-adapted version of the probabilistic instrumental learning task to assess reward-based decision-making that was adapted from the Pessiglione task (Halahakoon et al., 2024; Pessiglione et al., 2006). Participants were instructed that the goal of the task was to win as much money as possible by learning which abstract symbols were associated with a higher probability of winning money and which symbols were associated with a higher probability of avoiding a loss.

On each trial, two abstract symbols were presented on the screen. Each symbol was probabilistically associated with an outcome. One symbol was associated with a high probability (0.7) of an optimal outcome (winning money on win trials or avoiding a loss on loss trials) and a low probability (0.3) of the opposite outcome (no win or loss, respectively). The other symbol had reciprocal contingencies. Participants selected one symbol on each trial and received feedback indicating the outcome of their choice.

In the fMRI scanner, participants completed two runs of 60 trials each. Task timing was adjusted to accommodate the temporal constraints of the haemodynamic response. The inter-trial interval, during which an "X" was displayed on the screen was jittered using a flat distribution of 2-6 seconds. The interval between stimulus offset and outcome presentation was also jittered using a flat distribution of 2-5.5 seconds. To standardise response timing and slow task pace, participants were instructed to wait for a question mark to appear on the screen before making their selection. The total task duration was approximately 34 minutes (17 minutes per run). A schematic of the task and trial structure is shown in **Figure 5.1**.

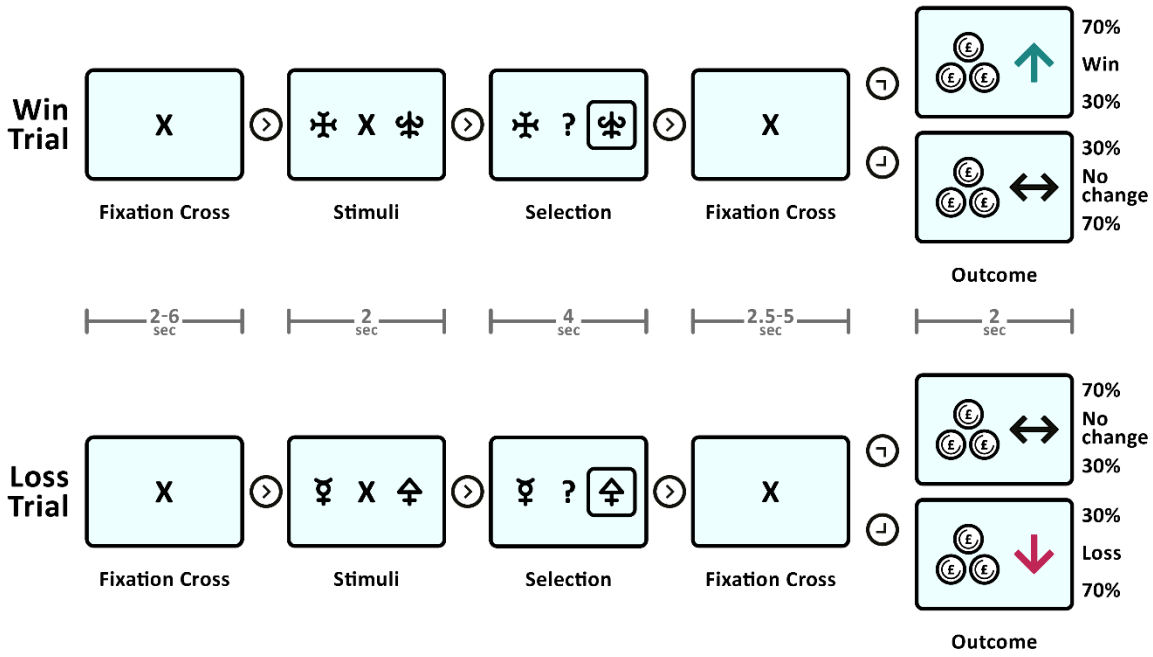


Figure 5.1. Schematic of the Probabilistic Instrumental Learning Task (PILT). Participants were informed that the goal of the task was to learn which symbols were associated with a higher probability of winning money or avoiding a loss. On each trial, two symbols were presented. Each symbol was associated with either a high probability (0.7) of a win or loss outcome and a low probability (0.3) of the opposite outcome (no-win or no-loss, respectively), with reciprocal contingencies across the symbol pair. In the fMRI scanner, participants completed two runs of 60 trials each. The inter-trial interval (fixation "X") was jittered using a flat distribution of 2-6 s. The intra-trial interval, defined as the period between stimulus offset and outcome presentation, was

jittered using a flat distribution of 2-5.5 s. Participants were instructed to wait for a question mark before selecting a symbol to slow and standardise response timing (illustrated in the selection panel).

Procedure

The study visit took place approximately one day after the infusion visit at the Oxford Centre for Human Brain Activity (OHBA), Warneford Hospital, Oxford **(Figure 5.2)**.

Upon arrival, participants completed practice trials of the PILT outside the scanner to ensure task comprehension and familiarisation with task requirements and response procedures in the scanner. The symbols presented within the practice trials were not shown in the scanner. Participants then underwent a standard MRI safety screening assessment prior to scanning.

MRI acquisition involved the collection of structural images, followed by completion of the PILT during functional MRI. The scanning session lasted approximately 90 minutes (see Chapter 3 for full details of the additional task administered in the scanner). Following the scan, participants completed clinical questionnaire measures.

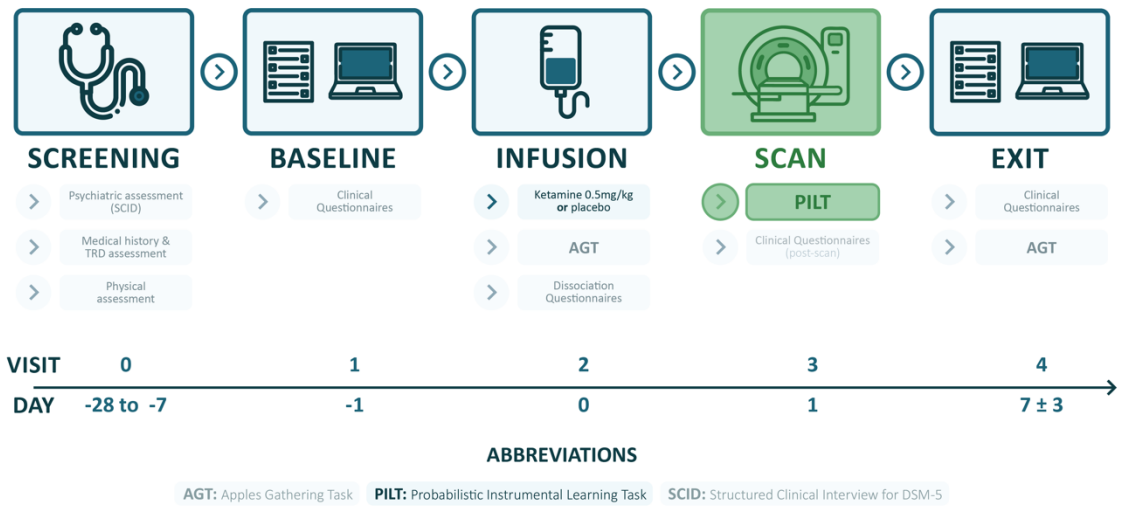


Figure 5.2. Schematic overview of the study design across visits. The Probabilistic

Instrumental Learning Task (PILT), highlighted in green, is the task examined in the analyses reported in this chapter.

Behavioural Methods

Behavioural data preparation

All behavioural pre-processing was performed while blind to group allocation. Custom MATLAB scripts were created and used to extract and process trial-level reward and loss data for each participant. No additional reaction-time exclusion criteria were applied, as the task itself had a minimum response delay prior to choice presentation **(Figure 5.1**). Participants were excluded if performance did not exceed chance levels defined as a proportion of advantageous choices below 0.5 in both the reward and loss conditions, indicating low task engagement or learning. Cleaned trial-level data, run-level datasets, and participant-level summary measures were saved for subsequent analyses.

Behavioural data analysis

The primary behavioural outcome was choice accuracy, defined as the proportion of advantageous choices i.e. selecting the stimulus associated with a 0.7 probability of a win outcome in the reward condition and selecting the stimulus associated with a 0.7 probability of avoiding a loss in the loss condition.

Accuracy data were analysed using mixed ANOVAs. To assess overall performance, accuracy across all trials was entered into a mixed ANOVA with Group (ketamine, placebo) as a between-subjects factor and Condition (reward, loss) as a within-subjects factor.

To examine learning-related changes in performance across the task, trials were divided into early and late trials, with late trials used to estimate asymptotic performance after learning had plateaued.

Accuracy was entered into a mixed ANOVA with Group as a between-subjects factor and Condition and Block (early, late) as within-subjects factors.

As an additional sanity check that the task produced consistent behaviour across repeated runs, learning across runs was examined using a linear mixed-effects model, with accuracy modelled as a function of Group, Condition, and Run, and random intercepts (and slopes for Run) included for each participant.

Reinforcement Learning Methods

A Rescorla-Wagner reinforcement learning (RW) model (Rescorla & Wagner, 1972; Behrens et al., 2007) was applied to the data. This model provides useful information on how participants update expectations about the association of stimuli with the outcomes according to the learning rule:

$$Q_{t+1}(s) = Q_t(s) + \alpha(R_t - Q_t(s))$$

where $Q_{t+1}(s)$ is the expected outcome probability of choosing optimal stimulus *s* in trial *t+1*, $\propto$ is the learning rate, and R_t is the outcome of the previous trial.

Choice probabilities were generated using a SoftMax action selector choice rule:

$$P_t(s) = \frac{1}{1 + e^{-\beta(Q_t(s) - Q_t(s'))}}$$

where $P_t(s)$ is the probability of choosing the optimal stimulus *s* in trial *t*, β is the inverse temperate parameter, and $Q_t(s)$ is the expected outcome probability of choosing the optimal stimulus *s* and $Q_t(s')$ is the expected outcome probability of choosing the suboptimal stimulus s'.

The initial expectancy i.e. the choice probabilities started at $Q_1(s) = 0.5$ for as either stimulus is equally likely at the start.

Model fitting

Model parameters were estimated separately for each participant and separately for win and loss trials. Parameter estimation followed a Bayesian approach in which the likelihood of observed choices was evaluated across a range of learning-rate and inverse-temperature values to obtain posterior probability distributions over parameters (i.e. the joint posterior over parameter combinations).

Missed trials were excluded from the choice likelihood and early trials occurring before the first informative outcome were excluded because outcomes could not yet be interpreted in terms of wins and losses. Parameter transformations were applied during fitting to ensure that learning rates remained bounded between 0 and 1 and that inverse-temperature values remained positive. Final parameter estimates were summarised as probability-weighted averages of the marginal posterior distributions, providing stable estimates that account for uncertainty in the model fit.

Neuroimaging Methods

MRI Data Acquisition

MRI scans were acquired on a 3T Siemens Prisma scanner using a 32-channel head-coil at Oxford Centre for Human Brain Activity (OHBA), University of Oxford. T1-weighted structural images were collected with 1mm isotropic (TR=1.9ms, TE= 3.97ms, Flip angle = 8°, FoV=192mm).

Functional images were acquired using T2*-weighted echo-planar imaging (EPI) sensitive to bold oxygen-level-dependent (BOLD) contrast. Each volume comprised 72 slices with 2mm isotropic resolution (TR = 1.5ms, TE= 25ms, Flip angle = 70°, FoV 216mm, multiband acceleration factor = 3 interleaved. Field maps were collected for distortion correction (TR=5.90ms, TE1=4.92ms

and TE2=7.38ms) and flip angle of 46°. Physiological data were recorded using a pulse oximeter and a respiratory belt (respiration) during scanning.

Data Retrieval and Organisation

All participant data (including structural, bold fMRI, field maps and task data) were retrieved from OHBA Calpendo system and organised in line with the Brain Imaging Data Structure (BIDS) which is a standardised organisational structure and is a common neuroimaging pipeline.

MRI Processing and Analysis

MRI data were processed and analysed using FSL (FMRIB Software Library v6.0) tools.

Initial Preprocessing of Structural and Functional Data

Pre-processing of the data was performed using FEAT (fMRI Expert Analysis Tool) within FSL. Separate pre-processing procedures were applied to the structural registration and analysis.

Structural Image Pre-processing

For each participant, the T1-weighted structural image was processed to ensure accurate segmentation and extraction of brain matter. The brain extraction was performed using SynthStrip, a tool specifically designed for high-quality brain extraction from structural MRI scans. Unlike traditional approaches such as BET, which relies primarily on intensity-based thresholding to remove non-brain tissues, SynthStrip uses a more advanced approach tailored for T1-weighted images, providing higher accuracy, particularly in populations with subtle anatomical differences and variability. SynthStrip produces a brain mask that isolates the brain from surrounding tissues, which is important for further registration and analysis. The final analysis included masks with CSF using a more flexible approach.

fMRI pre-processing

Pre-processing of the functional MRI data involved several key steps to prepare the images for statistical analysis. Motion correction was applied using MCFLIRT (Motion Correction FMRIB's Linear Image Registration Tool) in FSL. This was important due to head motion during scanning can lead to significant artifacts in functional data. To correct for distortions caused by magnetic field inhomogeneities in the functional scans, fieldmap-based B0 unwarping was applied. Each participant, a gradient-echo fieldmap was acquired, consisting of a phase-difference (RADS) image and a magnitude image. The magnitude image was brain-extracted and used to generate a mask for the fieldmap. These images were then used to estimate voxelwise magnetic field inhomogeneities, which were applied to unwarp the functional data. The effective EPI echo spacing and echo time were specified according to the acquisition protocol, with the echo spacing adjusted for the GRAPPA acceleration factor (but not the multiband factor). The unwarp direction was defined based on the phase-encoding direction in the fMRI protocol (anterior-posterior, corresponding to the -y axis). Following unwarping, the functional data were brain-extracted, spatially smoothed with a Gaussian kernel of 5mm full width at half maximum (FWHM), and temporally high-pass filtered to remove low-frequency drifts.

A high-pass temporal filter with a cut-off of 60s was applied to remove slow signal drifts, while no low-pass filtering was applied to capture high-frequency fluctuations related to the cognitive task.

Functional data were then registered to each participant's high-resolution structural (T1-weighted) image using boundary-based registration (BBR) in FSL. The participant's brain-extracted T1-weighted image was used as the structural reference. A linear (affine) registration with a normal search and BBR cost function was first applied to align the mean functional image to the participant's structural space. The structural image was then registered to the MNI152 standard space using a 12 degrees-of-freedom (DOF) affine transformation followed by nonlinear

registration (FNIRT) to account for individual differences in brain shape and size. The resulting transformations were applied to the functional data to bring them into standard space. Default warp resolution settings were used for the nonlinear step.

First-Level Analysis Setup in FEAT

Following the initial pre-processing, the first level analyses for each participant and for both runs were set up in FEAT within FSL. This process involves setting up the model that will be used to analyse the functional MRI data for each participant. Various models were performed which included runs separately, averaged and with and without motion correction parameters (see appendices for further details).

A general linear model (GLM) was applied to estimate single-subject task-related responses assuming a canonical hemodynamic response function. Single-subject design matrices included six motion parameters as regressors.

Creating event files for the PILT

For the PILT task, task condition effects were estimated using separate explanatory variables for the presentation of stimuli in win and loss trials (anticipation), and separate variables representing the four possible outcomes (2s period during presentation of win, no-win, loss or no-loss outcomes). An additional EV were included to account for a period of 30s where the task finished and the radiographer. This was modelled with each run.

EV contrasts

Once the task EVs were created contrasts were defined to analyse the effects of the task in the two groups (ketamine and placebo). These contrasts are important to understand which brain

regions were activated by different components of the task. Baseline contrasts were included as well.

1. Win anticipation > Baseline
2. Loss anticipation > Baseline
3. Win outcome > Baseline
4. Loss outcome > Baseline
5. No win outcome > Baseline
6. No loss outcome > Baseline
7. Win anticipation > Loss Anticipation
8. Loss Anticipation > Win Anticipation
9. Win outcome > Loss outcome
10. Loss outcome > Win outcome
11. Loss outcome > No loss outcome
12. No outcome > Loss outcome
13. Win outcome > No Win outcome
14. No win outcome > Win outcome

The contrast between 'win' vs 'no-win' outcomes, and 'no-loss' vs 'loss outcomes' were used as simple non-model-based measures of prediction error.

Modelling Task Runs

The PILT task was presented in two separate runs. Each run was pre-processed separately and modelled separately at the first level. For each participant, contrast estimates from the two runs were then combined using a fixed-effects model to produce a single average contrast per condition.

Intermediate-Level Analysis

Within each participant, first-level contrast images from the two runs were combined using a second-level fixed-effects FEAT analysis (level 2), yielding one contrast image per condition per participant.

Group-Level Analysis (All Participants)

Group-level analyses were performed using FSL's non-parametric permutation testing tool Randomise with 5000 permutations. This analysis assessed overall task-related effects across participants and tested for between-group differences. Statistical inference was conducted using threshold-free cluster enhancement (TFCE) with family-wise error correction at $p < 0.05$. The group-level general linear model included two groups (placebo and ketamine), with contrasts defined to test placebo > ketamine and ketamine > placebo effects.

Region of Interest (ROI) Analysis

Region of Interest analyses focused on striatal structures central to reinforcement and reward processing. Anatomical ROIs were defined using the Harvard-Oxford Structural Atlas. Four bilateral ROIs were created **(i)** left and right nucleus accumbens (ventral striatum) and **(ii)** left and right dorsal striatum, including caudate nucleus and putamen.

The nucleus accumbens is a core component of the mesolimbic reward circuitry and has been consistently implicated in the encoding of reward prediction errors (McClure et al., 2003; Pessiglione et al., 2006; Rutledge et al., 2010). In contrast, the dorsal striatum has been more strongly associated with action selection and instrumental learning from negative outcomes and punishment-related signals (Delgado et al., 2003; Jensen et al., 2003).

Although striatal involvement in reinforcement learning is well established, previous work has demonstrated dissociable encoding of reward and punishment signals across ventral and dorsal striatal subregions (O'Doherty, 2004; Seymour et al., 2007). Ventral and dorsal striatal ROIs were therefore analysed separately to examine potential functional dissociations in learning-related signalling.

In addition, the insula has been consistently implicated in aversive and punishment-related prediction error processing, as well as in encoding salience-weighted prediction error signals. Bilateral insula was therefore defined a priori for analyses of loss-domain prediction errors (D'Astolfo & Rief, 2017; Garrison et al., 2013; Kumar et al., 2018).

Small volume correction was performed within each ROI. Atlas-derived masks were thresholded at 50% probability (i.e. including all voxels with a probability of belonging to the ROI of at least 50%) and binarised prior to analysis. Significance within the anatomical mask was assessed using TFCE and Randomise.

Visualisation of Whole-Brain and ROI Results

To visualise the results, individual parameter estimates for significant clusters were extracted from the first-level statistical maps using FEATQuery (FSL).

Model-based fMRI regressors

To generate model-based regressors, expected value and reward prediction errors were estimated for each participant and each run by combining task timing information with trial-by-trial outputs from the RL model. Prediction errors for loss trials were sign-coded such that positive values reflected better-than-expected outcomes; in the loss condition this corresponds to no-loss

(avoidance) outcomes, whereas negative values reflected worse-than-expected outcomes (loss occurrence).

fMRI BOLD responses for each participant were modelled using regressors representing stimulus presentation during win and loss trials (anticipation; 2s) and outcome presentation during win and loss trials (outcome; 2s). Two parametric modulators were included at outcome, consisting of trial wise reward prediction errors (RPEs) for win and loss trials. RPE modulators were demeaned within each run. Six motion realignment parameters were included as nuisance regressors.

Trial RPEs were generated using a Rescorla–Wagner reinforcement learning model. Although the model also provided trial estimates of expected value during anticipation, expected value was not included as a parametric modulator in the fMRI analysis; anticipation periods were modelled using condition-based regressors only.

The following EVs were generated into the first-level analysis:

1. Win anticipation (base) - onset, duration, amplitude = 1
2. Loss anticipation (base) - onset, duration, amplitude = 1
3. Win outcome (base) - combined win/no-win trials
4. Loss outcome (base) - combined loss/no-loss trials
5. Win outcome RPE parametric modulator
6. Loss outcome RPE parametric modulator (positive = no-loss/avoidance)

All regressors were convolved with a canonical hemodynamic response function and entered into a first-level FEAT analysis together with motion parameters, using the same pre-processing pipeline as the non-computational condition-based GLM. Individual contrast images of interest

were computed at a participant level and entered into a second-level general linear model to examine within-group and between-group activations.

Results

The final analysis consisted of 53 participants (N=26 ketamine, N=27 placebo) after excluding one participant with poor task performance (<50% accuracy), one participant who experienced task failure, and one excluded due to image ghosting. Demographic and clinical characteristics are summarised in **Table 5.1**.

	Ketamine (N=26)	**Placebo (N=27)**
Sociodemographic variables		
Age years - mean ± SD	30.75 (10.62)	30.22 (9.99)
Female, n (%)	16 (62%)	20 (74%)
Years of education - mean ± SD	17.06 (2.78)	17.14 (2.83)
Ethnicity, n (%)		
White	22	19
Mixed/Multiple ethnic groups	2	1
Asian/Asian British	1	4
Black/African/Caribbean /Black British	1	-

Other ethnic group	-		1	

Clinical variables	Ketamine		Placebo	
	Pre-infusion	Post-infusion 24 hours	Pre-infusion	Post-infusion 24 hours
HAM-D	16.42 (4.13)	7.46 (3.83)	17.63 (2.82)	9.31 (5.11)
QIDS	17.65 (3.58)	7.77 (3.69)	18.07 (5.53)	10.07 (5.07)
TEPS Total	65.27 (12.18)	66.77(14.22)	68.44 (13.12)	70.37 (13.79)
Anticipatory	34.46 (6.46)	34.50(8.75)	34.74 (9.33)	35.89 (8.79)
Consummatory	30.81(6.41)	32.27(6.53)	33.70 (5.50)	34.48 (7.01)
GAD-7	10.00 (4.69)	2.65 (3.19)	10.19 (5.01)	2.96 (2.86)

Table 5.1. Demographic and questionnaire scores of the ketamine and placebo groups pre-infusion and post-infusion. This table includes final fMRI sample size only; full sample is reported in Chapter 3 (Methods). *2 participant missing (2 placebo) for ethnicity and years of education. Categories are based on the UK Office for National Statistics (ONS) 2021 classification. The "White" category includes participants identifying as English, Welsh, Scottish, Northern Irish or British, and those reporting any other White background (e.g., Polish, Russian, Portuguese, South African, European). The "Mixed/Multiple ethnic groups" category includes participants

identifying with more than one ethnic background (e.g., White and Black African, White and Asian, or other mixed combinations). Abbreviations: Hamilton Depression Rating Scale (HAM-D); Quick Inventory Depressive Symptomology (QIDS); The Temporal Experience of Pleasure Scale (TEPS); Generalised Anxiety Disorder-7 (GAD-7).

Behavioural performance on the PILT

Model free results

Choice accuracy on the PILT was defined as the proportion of advantageous choices made i.e. selecting the stimulus associated with a 0.7 probability of a win outcome in the reward condition and selecting the stimulus with 0.7 probability of 'no-loss' in the loss condition.

Accuracy data (proportion advantageous choices) were entered into a mixed ANOVA with Group (ketamine vs placebo) as a between-subjects factor and condition (reward vs loss) as a within-subjects factor. There was a main effect of valence [$F(1, 51) = 14.18$, $p < 0.001$, $\eta p^2 = < 0.001$], with higher accuracy in the win trials compared to the loss trials. However, there was no main effect of Group [$F(1, 51) = 0.08$, $p = 0.77$, $\eta p^2 = < 0.001$] nor a Group x valence interaction, [$F(1, 51) = 0.07$, $p = 0.80$, $\eta p^2 = < 0.001$] reflecting no significant differences in performance between the groups, see learning curves **(Figure 5.3).**

To examine learning across the task, accuracy was analysed using a mixed ANOVA with Group as a between-subjects factor and Condition (reward, loss) and Block (early, late) as within-subjects factors. This analysis revealed significant main effects of Condition [$F(1, 51) = 14.18$, $p = <0.01$, $\eta p^2 = 0.10$] and Block [$F(1, 51) = 34.01$, $p = <0.01$, $\eta p^2 = 0.04$]. There was a significant Condition × Block interaction [$F(1, 51) = 4.25$, $p = 0.04$, $\eta p^2 = 0.005$], indicating that changes in accuracy across trials differed between reward and loss trials. Accuracy increased more from early

to late trials for loss than reward trials, suggesting greater learning over time for loss trials. No interactions involving Group were observed. To assess task stability across runs, accuracy was examined using a linear mixed-effects model with Run as a predictor. There was no main effect of Run [$F(1, 108) = 0.003$, $p = 0.95$] and no interactions with Group or Condition, suggesting stable performance across runs $p > 0.05$.



Figure 5.3. Learning curves for reward and loss conditions of the Probabilistic Instrumental Learning Task. Mean proportion of advantageous choices is shown across trials for the ketamine and placebo groups. Accuracy was averaged across participants and runs and plotted by trial number within each condition (1-30). Error bars denote SEM.

Model based results

Computational parameters were entered separately (learning rate and inverse temperature) into a mixed ANOVA with Group (ketamine vs placebo) as a between-subjects factor and condition (reward vs loss) as a within-subjects factor. For learning rate, there was a significant main effect of

valence [$F(1, 51) = 8.13, p = 0.01, \eta p^2 = 0.14$], with higher learning rates for loss compared to win trials (**Figure 5.4**). There was no main effect of group [$F(1, 51) = 0.16, p = 0.7, \eta p^2 = <0.001$] and no group x valence interaction, suggesting that learning rate did not differ significantly between the group and that the valence-related difference were similar across groups. A similar pattern was observed for inverse temperature, with a significant main effect of valence [$F(1, 51= 26.85, p = < 0.001, \eta p^2 = 0.34$] with higher inverse temperature for win compared to loss trials **(Figure 5.5).** However, there was no main effect of group [$F(1, 51) = 0.63, p = 0.43, \eta p^2 = 0.01$] and no group x valence interaction [$F(1, 51) = 2.06, p = 0.2, \eta p^2 = 0.04$].

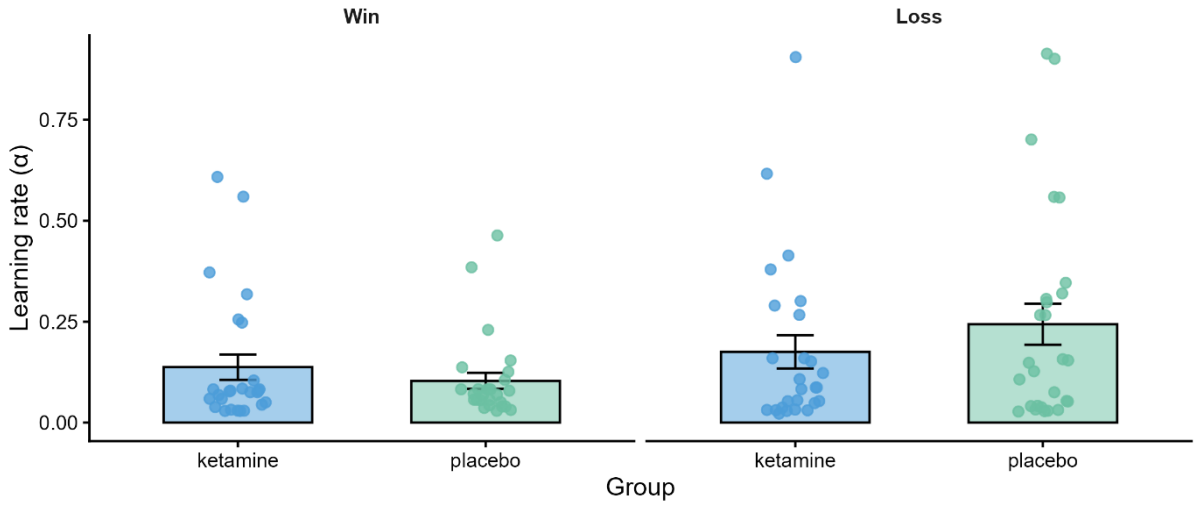


Figure 5.4. Learning rates during the PILT in the ketamine and placebo groups. Error bars represent the standard error of the mean and points represent individual participants.

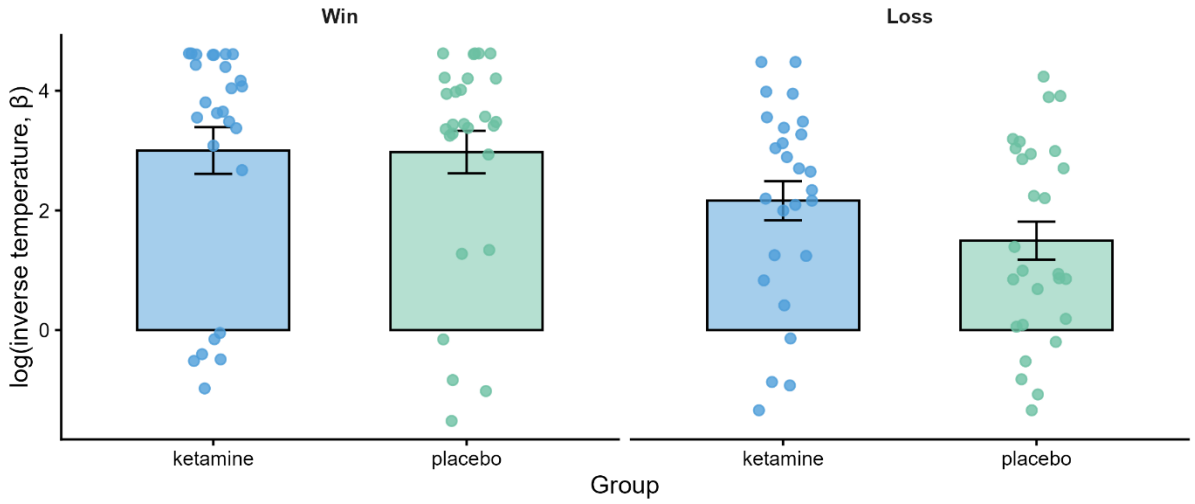


Figure 5.5. Inverse temperature estimates during the PILT in the ketamine and placebo group. Error bars represent the standard error of the mean and points represent individual participants.

fMRI results

Whole Brain analysis

Main effect of task (all participants)

To confirm that the task engaged brain regions previously associated with reward processing, a whole brain analysis was conducted across all participants and conditions. Significant activation was observed in reward regions including the striatum (both ventral and dorsal), thalamus, insular, hippocampus and amygdala. The breakdown of activation by task contrast and cluster is provided below **(Tables 5.2-5.5 and Figures 5.6-5.9).**

Anticipation phase

Win trials

Across all participants, win anticipation relative to baseline had significant activation within striatal regions (putamen, caudate, nucleus accumbens and ventral striatum), alongside anterior insula and thalamus (65,964 voxels, peak voxel location: x = -28, y = -72, z = -58, t = 3.30, p <0.001) with additional cerebellum activation (48 voxels, peak voxel location: x = -18, y = -40, z = -44, t = 5.49, p = 0.03). This anticipatory activation pattern is consistent with previous findings in neural responses in similar reward paradigms (Haber & Knutson, 2010; Knutson et al., 2001).

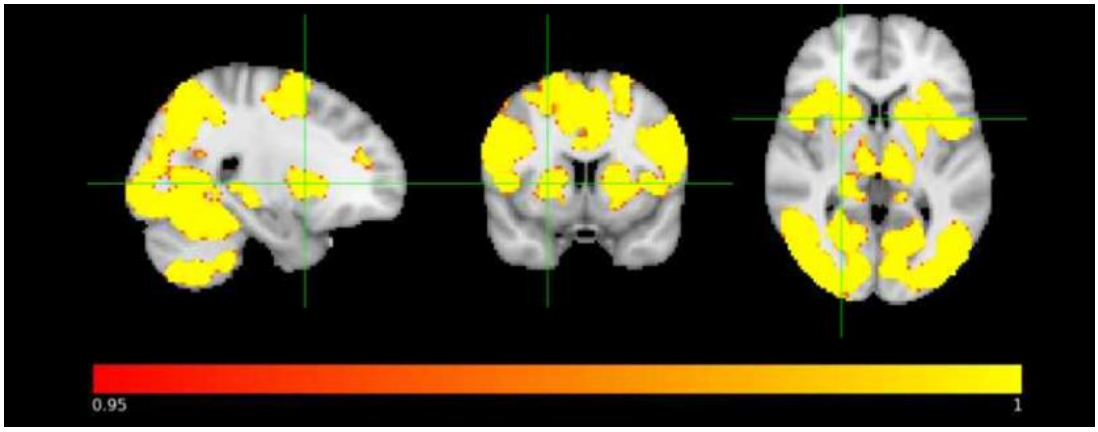
Loss trials

Loss anticipation similarly engaged dorsal striatum (putamen/caudate), insula and thalamus (66,508 voxels, peak voxel location: x = 28, y = -60, z = -58, t = 3.14, p <0.001). Ventral striatal/nucleus accumbens activation did not survive correction for this contrast. Full statistical results are reported in **Table 5.2** and thresholded activation maps are shown in **Figure 5.6**. Meta-analysis on incentive tasks also supports overlapping engagement of striatum-insula-thalamus networks during both win and loss anticipation (Chen et al., 2022).

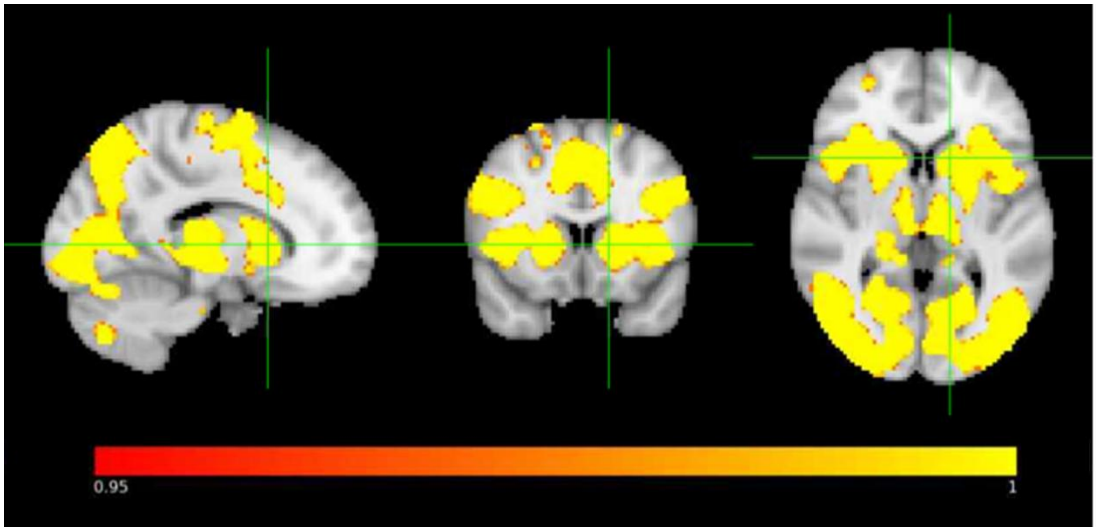
Differential contrasts

The win anticipation > loss anticipation showed significant activation in frontal pole (459 voxels, peak voxel location: x= -4, y = 64, z = -0, t = 5.90, p = 0.02) and medial frontal cortex (63 voxels, peak voxel location: x = -4, y = 64, z = -0, t = 4.86, p = 0.04) with additional occipital engagement (33 voxels, peak voxel location: x= -52, y= -76, z= 26, t = 5.36, p = 0.04). Other regions within significant clusters are listed in **Table 5.2** and thresholded activation maps are shown in **Figure 5.6.** Loss anticipation > win anticipation showed significant activation in occipital and posterior parietal cortices (2,631 voxels, peak voxel location: x = -30, y = -62, z = 50, t = 5.82, p = 0.02).

A) Win anticipation



B) Loss anticipation



C) Win anticipation > loss anticipation

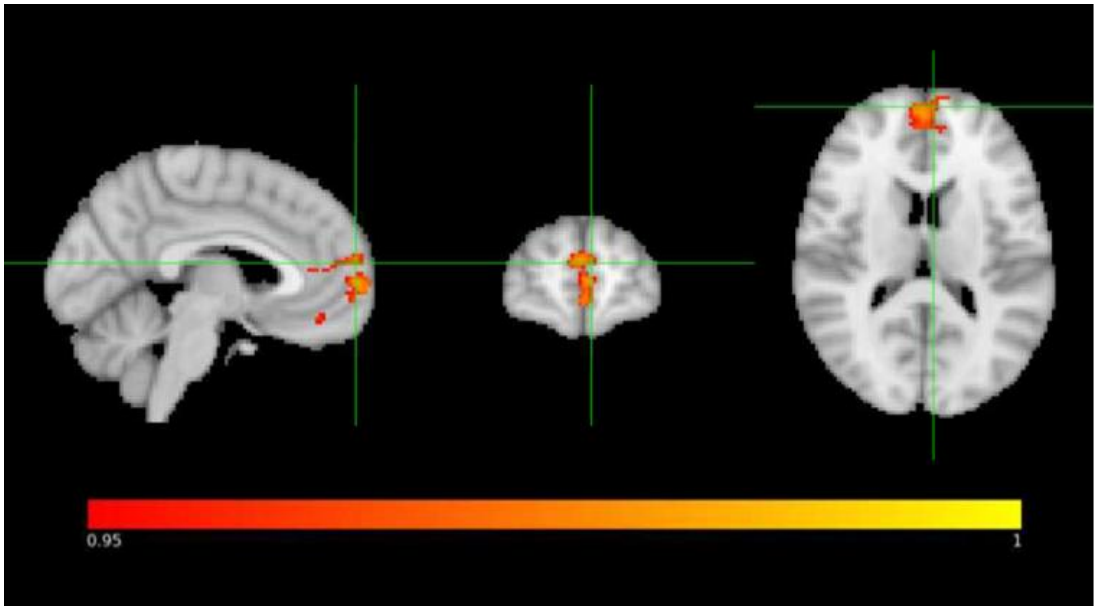


Figure 5.6. Whole brain activation patterns for main effect of task in the anticipation phase. **(A)** Sagittal, coronal, and axial images depicting significantly increased BOLD activation during win anticipation relative to baseline, in a whole range of areas including the cerebellum, frontal pole, putamen, hippocampus and insula (see full list in **Table 5.2**). The cursor is positioned in the right putamen (MNI coordinates: [x = 24, y = 8, z = 4]). **(B)** Sagittal, coronal, and axial images depicting significantly increased BOLD activation during loss anticipation relative to baseline in a whole range of areas including the dorsal striatum (putamen/caudate), insula and thalamus (see full list in **Table 5.2**). The cursor is positioned in the left caudate (MNI coordinates: [x = -14, y = 14, z= 4]). **(C)** Sagittal, coronal, and axial images depicting significantly increased BOLD activation during win anticipation relative to loss anticipation in the frontal pole and medial frontal cortex (see full list in **Table 5.2**). The cursor is positioned in the left frontal pole (MNI coordinates: [x= -4, y = 61, z = 14]. Results are threshold-free cluster enhancement (TFCE) corrected, with a family-wise error cluster significance of $1 - p > 0.95$.

Cluster index	**Brain area**	**Cluster size (voxels)**	**MNI max (x, y, z)**			***TFCE***	***tscore***
Win anticipation > Baseline							
1	Cerebellum encompassing frontal pole, middle frontal gyrus, putamen, precentral gyrus, brainstem, occipital	65,964	-28	-72	-58	1	3.30

	cortex, precuneus, hippocampus, insula, anterior cingulate gyrus, right caudate, temporal fusiform cortex, PCC, ACC, thalamus, motor cortex						
2	Cerebellum	48	-18	-40	-44	0.974	5.49
Loss anticipation > Baseline							
	Cerebellum, encompassing thalamus, occipital, intracalcarine cortex, precuneous, PCC, brainstem,						
1	temporal fusiform cortex, ACC, motor cortex, putamen, caudate, postcentral gyrus, precentral gyrus, insula	66,508	28	-60	-58	1	3.14
Win anticipation > loss anticipation							
	Frontal pole,						
1	paracingulate gyrus, cingulate gyrus anterior	459	-4	64	0	0.981	5.90

	division, frontal medial cortex,						
2	Frontal medial cortex, subcallosal cortex, paracingulate cortex, cingulate gyrus anterior	63	-2	40	-16	0.959	4.86
3	Lateral occipital cortex	33	-52	-76	26	0.958	5.36
Loss anticipation > win anticipation							
1	Lateral occipital cortex, occipital fusiform gyrus, supramarginal gyrus, anterior division, angular gyrus, superior parietal lobule, temporal occipital fusiform cortex	2,631	-30	-62	50	0.997	5.82
2	Lateral occipital cortex, precuneous cortex, superior parietal lobe, angular gyrus	2,302	34	-76	22	0.991	5.58
3	Paracingulate, superior frontal gyrus, cingulate gyrus anterior division	724	-2	16	46	1	6.93
4	Middle frontal gyrus and superior frontal gyrus	21	30	4	52	0.959	5.82

5	Temporal fusiform cortex and temporal occipital fusiform cortex	11	-40	-44	-22	0.952	4.07

Table 5.2. Main effect of task - anticipation phase (whole-brain). Whole-brain clusters showing significant activation for the main effect of task for the anticipation phase contrasts. Cluster index, anatomical label, cluster size (voxels), peak MNI coordinates, threshold-free cluster enhancement (TFCE) value and peak t-statistic. Results are corrected for multiple comparisons (5000 permutations).

Outcome phase

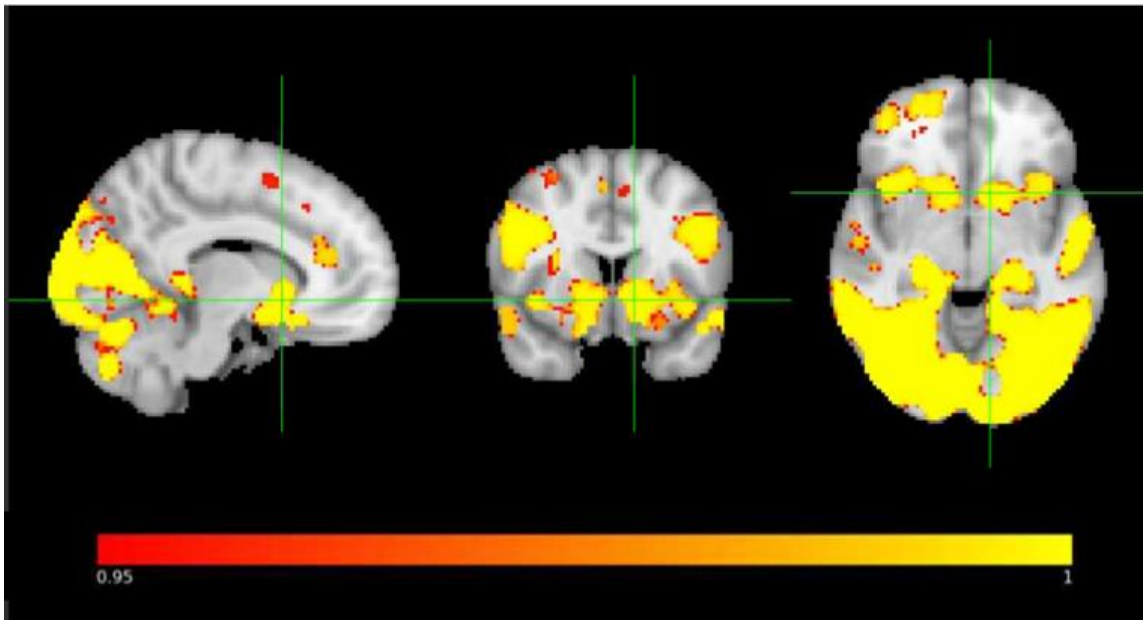
Win trials

Win outcome relative to baseline revealed significant activation in striatal regions (putamen, caudate, nucleus accumbens) as well as insula and thalamus with additional engagement in the cerebellum (57,710 voxels, peak voxel location: x = -28, y = -74, z = -54, t = 4.85, p <0.001) and cingulate cortex (494 voxels, peak voxel location: x = 4, y=-34, z = 28, t =7.29 , p <0.01), middle frontal gyrus (266 voxels, peak voxel location: x = 32, y = 6, z = 58, t =5.65 , p <0.01) ACC (222 voxels, peak voxel location: x = 4, y = 0, z = 30, t = 6.95 , p <0.01). This is consistent with prior findings that reward responses implicating cortico-striatal circuitry in reward processing. The no-win outcome relative to baseline revealed significant activation across a distributed network of regions including the cerebellum, posterior cingulate gyrus, precuneus cortex, frontal pole, middle frontal gyrus, parahippocampal gyrus, occipital cortex, hippocampus, thalamus, postcentral gyrus, temporal fusiform cortex, supramarginal gyrus. Full statistical results are reported in **Table 5.3** and thresholded activation maps are shown in **Figure 5.7**.

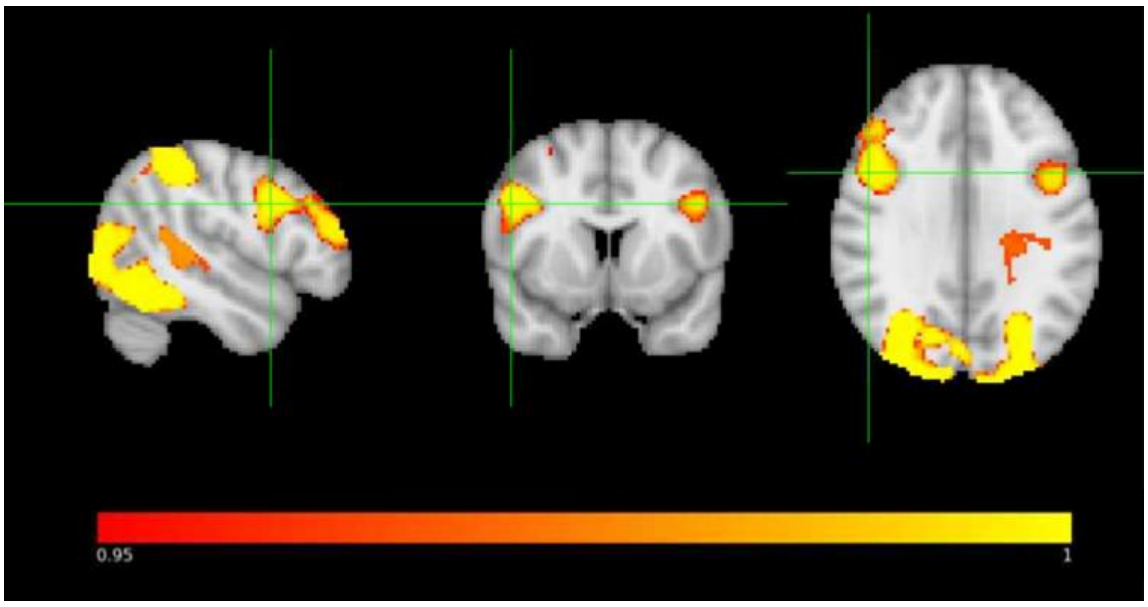
Differential Contrasts

The win outcome > no-win outcome contrast revealed significant activation in the ventral and dorsal striatum, including the nucleus accumbens, caudate and putamen, as well as the anterior and posterior cingulate cortex. Full statistical results are reported in **Table 5.3** and thresholded activation maps are shown in **Figure 5.7**. No clusters for the no-win outcome > win outcome contrast survived correction for multiple comparisons.

A) Win outcome > baseline



B) No Win outcome > baseline



C) Win outcome > no win outcome

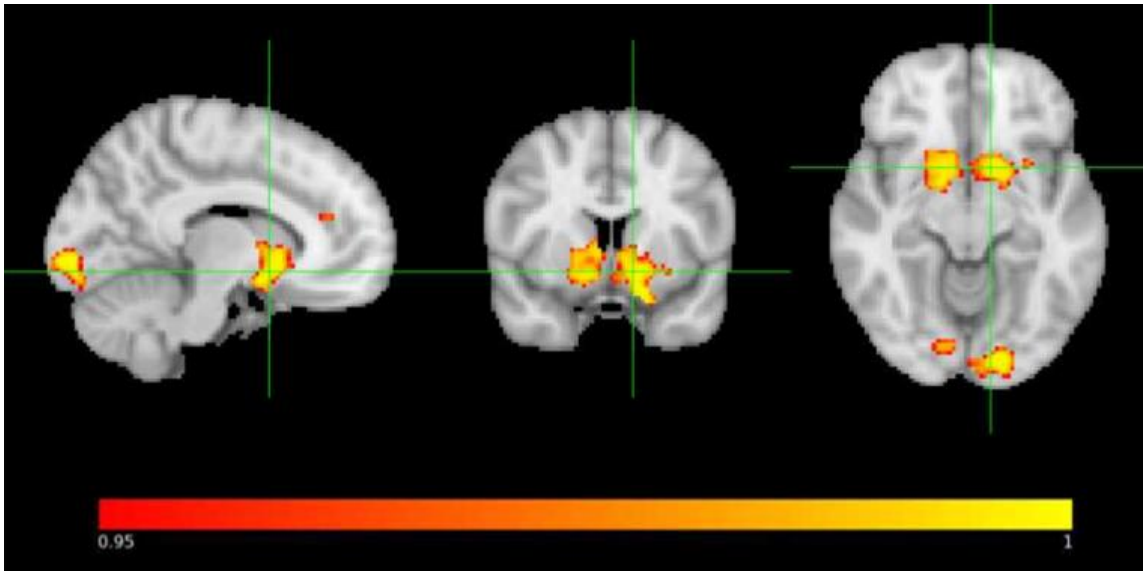


Figure 5.7. Whole brain activation patterns for main effects of task in the win outcome phase. (A) Sagittal, coronal, and axial images depicting significantly increased BOLD activation during win outcome, in a whole range of areas including cerebellum, hippocampus, thalamus and frontal orbital cortex (see full list in **Table 5.3**). The cursor is positioned in the left nucleus accumbens (MNI coordinates: [x = -11, y = 13, z = -6]). **(B)** Sagittal, coronal, and axial images depicting significantly increased BOLD activation during no win outcome, in a whole range of areas including Cerebellum including posterior cingulate gyrus, precuneus, and parahippocampal gyrus (see full list in **Table 5.3**). The cursor is positioned in the right pre-central gyrus (MNI coordinates: [x = 50, y = 10, z = 30]). **(C)** Sagittal, coronal, and axial images depicting significantly increased BOLD activation win outcome relative to no win outcome, in a whole range of areas including occipital fusiform gyrus, frontal orbital cortex, nucleus accumbens, caudate and putamen (see full list in **Table 5.3**). The cursor is positioned in the left nucleus accumbens (MNI coordinates: [x = -11, y = 8, z = -9]). Results are threshold-free cluster enhancement (TFCE) corrected, with a family-wise error cluster significance of $1 - p > 0.95$.

Cluster index	Brain area	Cluster size (voxels)	MNI max (x, y, z)			*TFCE*	*tscore*
Win outcome > baseline							
1	Cerebellum, occipital pole, lingual gyrus, temporal occipital fusiform, parahippocampal, hippocampus, thalamus, frontal orbital cortex, nucleus accumbens, caudate, putamen, insular cortex, temporal pole, brainstem, subcallosal cortex, ACC, paracingulate gyrus, amygdala	57,710	-28	-74	-54	1	4.85
2	Posterior cingulate cortex	494	4	-34	28	0.999	7.29
3	Middle frontal gyrus	266	32	6	58	0.986	5.65
4	ACC	222	4	0	30	0.992	6.95
5	Cerebellum	80	30	-72	-50	0.983	6.58
6	Cerebellum	69	8	-78	-38	0.991	8.09
No win outcome > baseline							

1	Cerebellum including posterior cingulate gyrus, precuneous cortex, parahippocampal gyrus, occitpital cortex, hippocampus, thalamus, postcentral gyrus, inferior temporal gyrus, temporal fusiform cortex, supramarginal gyrus	33,802	-10	-78	-42	1	3.96
2	Right Precentral gyrus and inferior frontal gyrus, middle frontal gyrus, frontal pole	1,805	50	10	30	1	7.52
3	Left Precentral gyrus, inferior frontal gyrus, middle frontal gyrus,	499	-46	8	30	0.996	7.10
4	Hippocampus and parahippocampal	152	-22	-28	-6	0.961	4.49
5	Cerebellum	64	10	-78	-38	0.98	6.84
6	Middle frontal gyrus	22	30	6	56	0.955	5.49

7	Frontal pole	11	22	60	-6	0.953	5.26
Win outcome > no win outcome							
1	Occipital fusiform gyrus, lingual gyrus, intraclcarine cortex	1,315	16	-90	0	1	10.19
2	Frontal orbital cortex, left nucleus accumbens, left caudate, left putamen, left subcallosal cortex, left insular, left amygdala	703	-16	8	-20	1	7.55
3	Right nucleus accumbens, right amygdala, right putamen, right caudate,	644	14	2	-12	0.996	7.37
4	Cingulate gyrus anterior and paracingulate gyrus	509	0	36	18	0.955	4.98
5	Cingulate gyrus posterior	95	-2	-26	36	0.953	4.91
6	Left cingulate gyrus anterior	23	0	-10	34	0.95	4.17
7	Frontal pole	17	-2	62	6	0.98	4.60
8	Left cingulate gyrus anterior	1	0	6	32	0.992	4.20

Table 5.3. Main effect of task - win and no-win outcome phase (whole-brain). Whole-brain clusters showing significant activation for the main effect of task win and no-win outcome

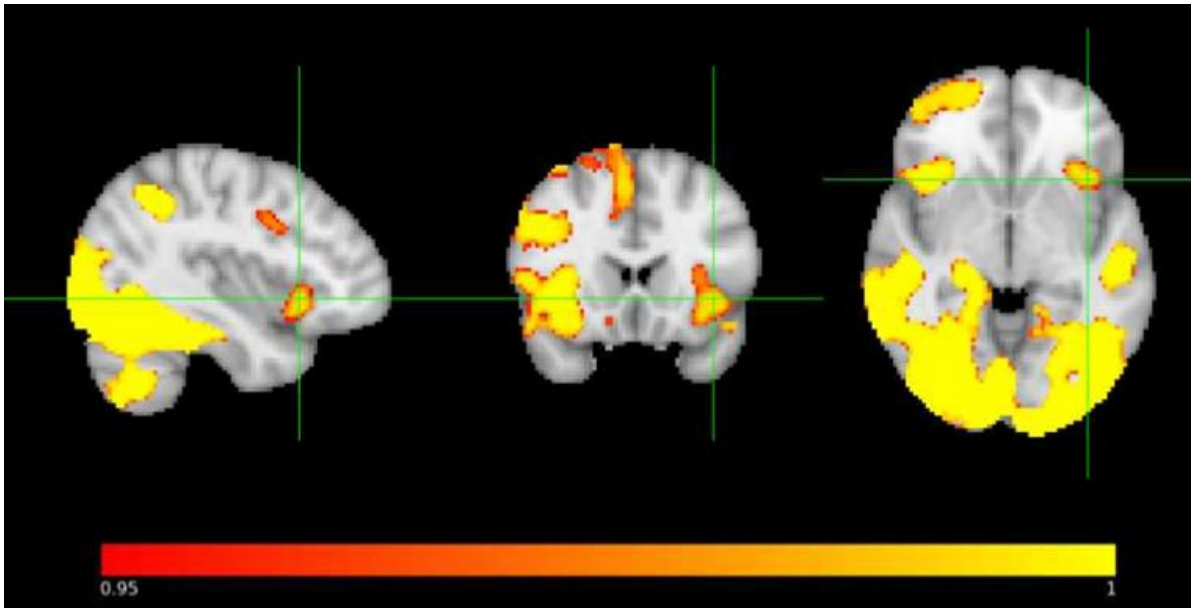
contrasts. Cluster index, anatomical label, cluster size (voxels), peak MNI coordinates, TFCE value and peak t-statistic are reported. Results are corrected for multiple comparisons (5000 permutations).

Loss trials

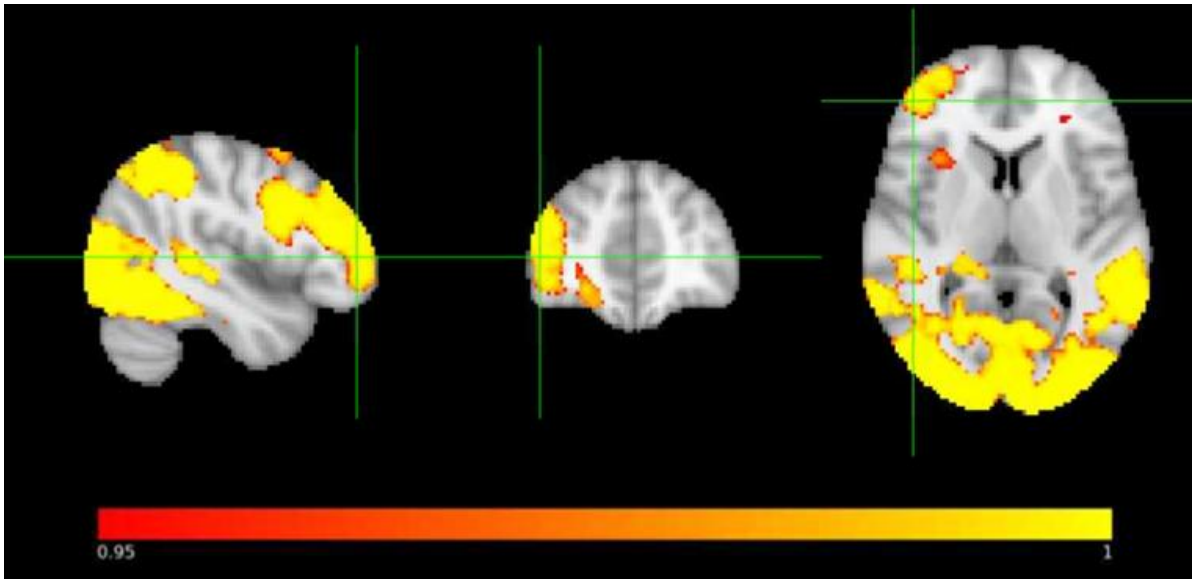
Loss outcome relative to baseline engaged insula and thalamus, with additional activation in medial/orbital frontal regions and hippocampal areas **(Table 5.4)** A similar overall activation pattern was observed for no-loss relative to baseline **(Table 5.4).** These regions have been implicated in punishment processing and outcome valence processing in instrumental reinforcement learning paradigms. (O'Doherty, 2004; Seymour et al., 2007).

Loss outcome relative to no loss outcome showed significant activation in the frontal and insular/orbital regions. Full details are provided in **(Table 5.4).** No loss outcome > loss outcome showed greater activation in striatal/subcallosal regions (putamen, caudate, subcallosal cortex clusters (15,001 voxels, peak voxel location: x = 24, y = -8, z = 28, t = 5.54, p <0.01). Full statistical results are reported in **Table 5.4** and thresholded activation maps are shown in **Figure 5.8.**

A)Loss outcome > baseline



B)No loss outcome > baseline



C)Loss outcome > no loss outcome

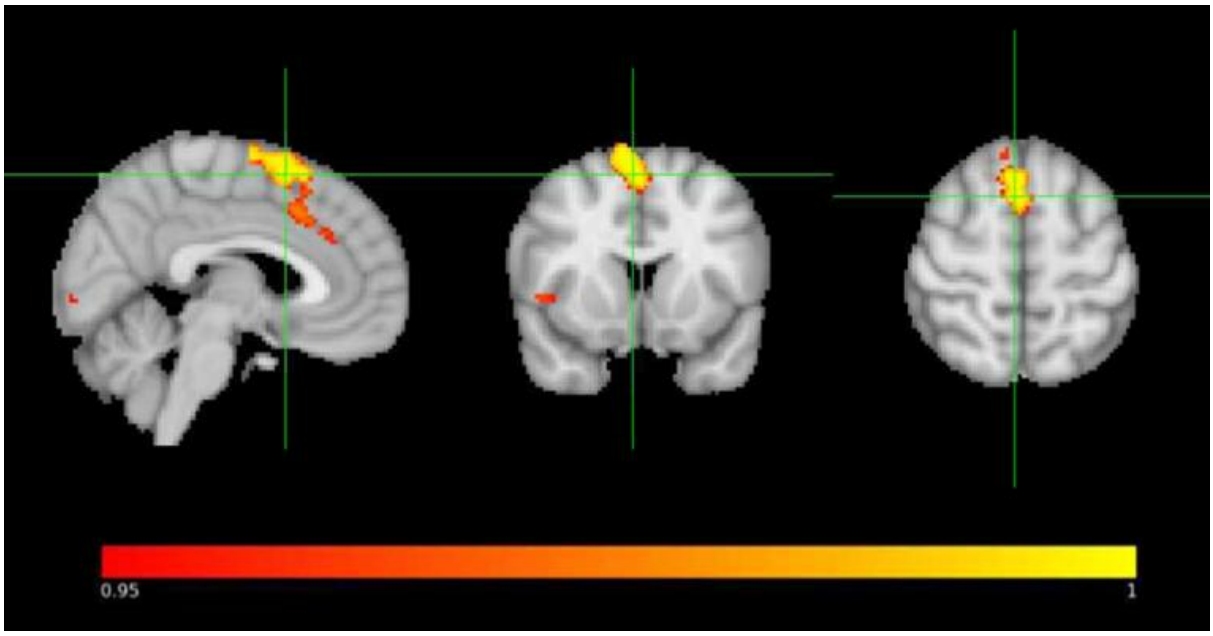


Figure 5.8. Whole brain activation patterns for loss outcome phase. (A) Sagittal, coronal, and axial images depicting significantly increased BOLD activation during loss outcome relative to baseline, in a whole range of areas including cerebellum, occipital fusiform cortex and thalamus (see full list in **Table 5.4**). The cursor is positioned in the left insular cortex (MNI coordinates: [x = -38, y = 18, z = -4]). **(B)** Sagittal, coronal, and axial images depicting significantly increased BOLD activation during no loss outcome relative to baseline, in a whole range of areas including

cerebellum, lateral occipital cortex, precuneus, hippocampus and putamen (see full list in **Table 5.4**). Cursor in the right frontal pole MNI coordinates: x = 46, y = 46, z = 6. **(C)** Sagittal, coronal, and axial images depicting significantly increased BOLD activation loss outcome relative to no loss outcome, in a whole range of areas including superior frontal gyrus, middle temporal gyrus, occipital and insular cortex **(see full list in Table 5.4**). Cursor is positioned in the right superior frontal gyrus (MNI coordinates: [x = 4, y = 12, z = 58]). Results are shown threshold-free cluster enhancement (TFCE)-corrected with a family-wise error cluster significance of $1 - p > 0.95$.

Cluster index	**Brain area**	**Cluster size (voxels)**	**MNI max (x, y, z)**			***TFCE***	***tscore***
Loss outcome > baseline							
1	Cerebellum, inferior temporal gyrus, middle temporal gyrus, angular gyrus, temporal occipital fusiform cortex, occipital pole, lingual gyrus, brainstem, right hippocampus, superior parietal lobe, thalamus, parahippocampal gyrus	35,004	-30	-72	-58	1	4.03
2	Insular cortex, subcallosal cortex, frontal orbital cortex, frontal pole,	7,709	40	16	-8	1	6.81

Cluster index	Brain area	Cluster size (voxels)	MNI max (x, y, z)			*TFCE*	*tscore*
	middle frontal gyrus, paracingulate gyrus, cingulate gyrus anterior, frontal pole, superior frontal gyrus						
3	Insular cortex and frontal orbital cortex	512	-38	18	-4	0.995	6.24
4	Precentral gyrus and middle frontal gyrus	258	-42	4	34	0.994	7.05
5	Cingulate gyrus posterior division	38	2	-30	28	0.961	5.88
6	Precentral gyrus	2	-52	2	52	0.951	5.37
No loss outcome > baseline							
1	Cerebellum, lateral occipital cortex, intracalcarine cortex, precuneus cortex, occipital fusiform cortex, lingual gyrus, temporal occipital fusiform cortex, precentral gyrus, hippocampus, thalamus,	42,533	-32	-70	-56	1	3.63

Cluster index	Brain area	Cluster size (voxels)	MNI max (x, y, z)			*TFCE*	*tscore*
	parahippocampal gyrus posterior, brainstem						
2	Frontal pole, insular, putamen, frontal orbital cortex, middle frontal gyrus, subcallosal cortex	5,820	46	46	6	1	5.49
3	Cingulate gyrus posterior	43	6	-34	28	0.95	4.60
4	Hippocampus	27	-20	-30	-10	0.95	3.61
5	Cerebral white matter	7	-28	38	6	0.95	3.52
6	Cerebellum	1	-6	-60	-54	0.95	3.61
7	Cingulate gyrus, anterior	1	4	-4	30	0.95	4.96
Loss outcome > no loss outcome							
1	Superior frontal gyrus, motor cortex, paracingulate gyrus, cingulate gyrus anterior	868	4	12	58	0.99	6.85
2	Insular cortex, frontal operculum cortex and inferior frontal gyrus	121	36	20	4	0.97	5.55

Cluster index		Brain area	Cluster size (voxels)	MNI max (x, y, z)			*TFCE*	*tscore*
	3	Occipital pole	55	14	-90	2	0.97	5.62
	4	Intracalcarine cortex	42	36	31	40	0.96	5.28
	5	Middle temporal gyrus	32	54	-36	0	0.97	6.08
	6	Intracalcarine cortex	23	-12	-68	8	0.96	5.89
	7	Insular cortex and frontal orbital cortex	17	36	16	-12	0.957	5.43
	8	Middle temporal gyrus	14	50	-26	-6	0.959	5.69
	9	Inferior frontal gyrus	2	50	20	-6	0.952	5.22
No loss outcome > loss outcome								
	1	Left and right nucleus accumbens, caudate, putamen, subcallosal cortex, postcentral gyrus, precentral gyrus, frontal pole, frontal medial cortex, frontal orbital cortex, occipital cortex, superior parietal lobe, cerebral white matter	15,001	24	-8	28	0.997	5.54

Cluster index	Brain area	Cluster size (voxels)	MNI max (x, y, z)			*TFCE*	*tscore*
2	Superior frontal gyrus, middle frontal gyrus	1,133	-22	28	46	0.983	4.53
3	Right occipital cortex	493	52	-70	8	0.975	4.64
4	Middle temporal gyrus	56	-58	-18	-16	0.958	4.24
5	Middle temporal gyrus	55	-56	-46	-10	0.958	4.08
6	Planum temporale	23	-60	-38	10	0.953	3.77
7	Left occipital cortex	14	-42	-78	2	0.954	3.78
8	Left superior temporal gyrus	1	-68	-20	6	0.951	4.13

Table 5.4. Main effect of task – loss and no loss outcome (whole-brain). Whole-brain clusters showing significant activation for the main effect of task loss and no loss outcome contrasts. Cluster index, anatomical label, cluster size (voxels), peak MNI coordinates, TFCE value and peak t-statistic are reported. Results are corrected for multiple comparisons (5000 permutations).

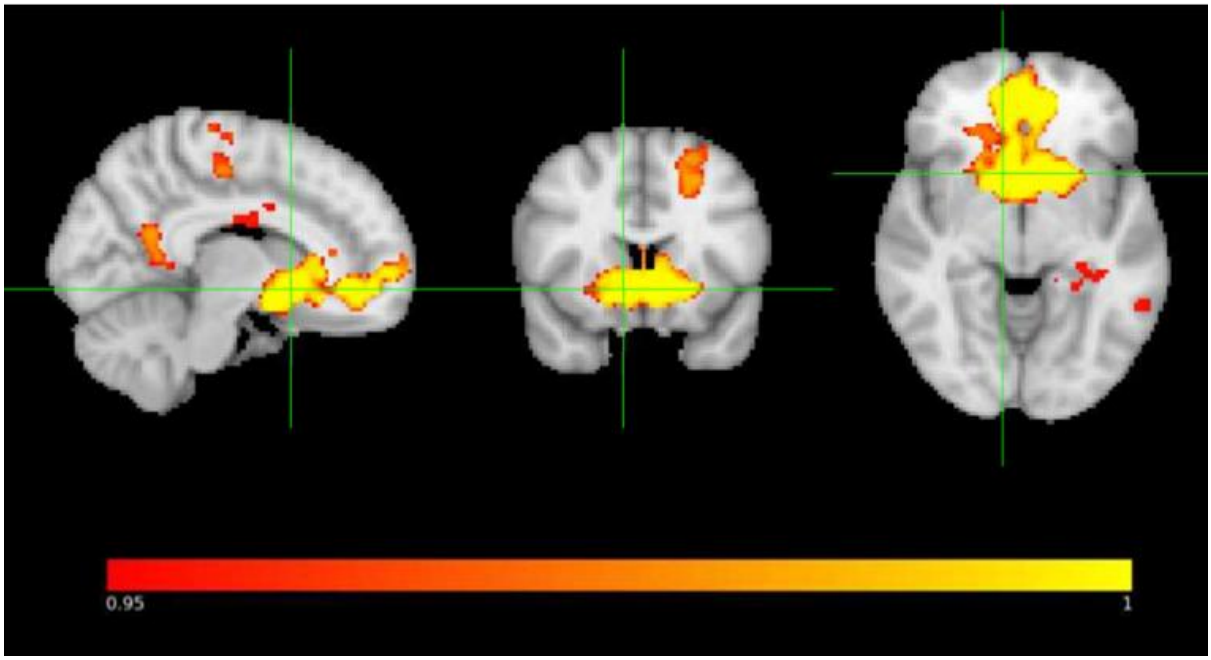
Outcome valence contrasts

Win outcome > loss outcome

Win outcome relative to loss outcomes showed greater activation in striatal regions (including nucleus accumbens, caudate and putamen), as well as the thalamus, hippocampus, cingulate cortex and orbitofrontal engagement **(Table 5.5).** Loss outcomes relative to win outcomes showed

greater activation in fronto-parietal regions, including the superior frontal gyrus and angular gyrus (**Table 5.5**). Thresholded activation maps are shown in **Figure 5.9.**

A)Win outcome > loss outcome



B) Loss outcome > win outcome

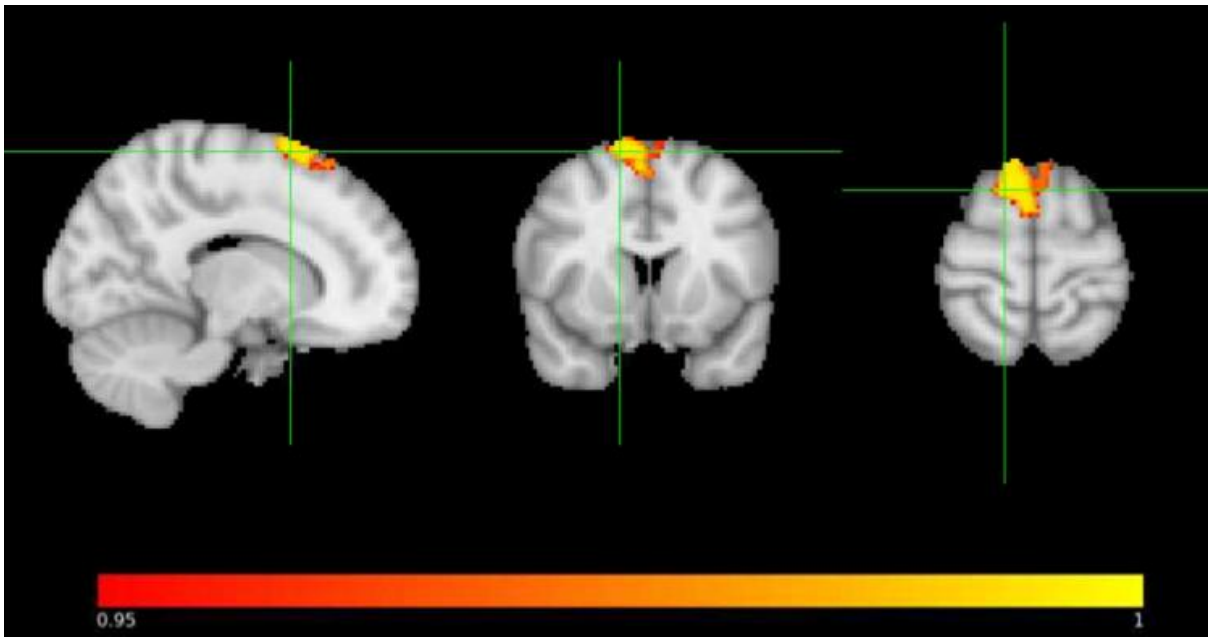


Figure 5.9. Whole brain activation patterns for outcome valence contrasts. (A) Sagittal, coronal, and axial images depicting significantly increased BOLD activation during win outcome

relative to loss outcome, in a whole range of areas including medial frontal cortex, nucleus accumbens, caudate, hippocampus and thalamus (see full list in **Table 5.5**). The cursor is positioned in the right nucleus accumbens (MNI coordinates: [x = 9, y = 13, z = -6]). **(B)** Sagittal, coronal, and axial images depicting significantly increased BOLD activation during loss outcome relative to win outcome. The cursor is positioned in the right superior frontal gyrus (MNI coordinates: [x = 14, y = 22, z = 66]). Results are shown threshold-free cluster enhancement (TFCE)-corrected with a family-wise error cluster significance of $1 - p > 0.95$.

Cluster index	**Brain area**	**Cluster size (voxels)**	**MNI max (x, y, z)**			***TFCE***	***tscore***
Win outcome > loss outcome							
1	Frontal medial cortex, subcallosal cortex. nucleus accumbens, caudate, putamen, hippocampus, amygdala, frontal pole, cingulate gyrus anterior, paracingulate gyrus	6,693	-2	32	-20	1	5.59
2	Postcentral gyrus, precentral gyrus, parietal operculum cortex, superior frontal gyrus	5,882	38	-28	42	0.998	5.50
3	Cingulate gyrus posterior and precuneous cortex	2,101	-6	-52	22	0.994	5.61

Cluster index	Brain area	Cluster size (voxels)	MNI max (x, y, z)			*TFCE*	*tscore*
4	Hippocampus, thalamus, parahippocampal gyrus posterior, inferior temporal gyrus	647	-16	-38	-2	0.964	4.32
5	White matter and cingulate gyrus anterior	367	20	-24	28	0.961	3.84
6	Postcentral gyrus and supramarginal gyrus anterior	231	-44	-36	48	0.969	5.00
7	Left occipital cortex	196	-40	-74	30	0.967	4.88
8	Frontal orbital cortex	152	59	78	31	0.964	2.03
9	Middle temporal gyrus	65	-58	-18	-18	0.957	4.15
10	Cingulate gyrus anterior and white matter	58	16	4	30	0.954	3.41
11	Frontal pole	55	-38	38	10	0.955	3.91
12	Superior temporal gyrus left	14	-68	-20	4	0.954	4.80
13	Inferior temporal gyrus	6	-58	-58	-16	0.951	3.19
14	Occipital pole left	5	-24	-90	20	0.95	3.83
15	Inferior temporal gyrus	2	-50	-60	-12	0.95	2.93

Cluster index	Brain area	Cluster size (voxels)	MNI max (x, y, z)			*TFCE*	*tscore*
Loss outcome > win outcome							
1	Superior frontal gyrus	890	14	12	66	0.998	6.84
2	Angular gyrus	49	60	-48	40	0.956	5.11
3	Superior frontal gyrus	41	2	46	38	0.961	5.10

Table 5.5. Main effect of task – outcome valence contrasts (whole-brain). Whole-brain clusters showing significant activation for the main effect of task for the outcome valence contrasts. Cluster index, anatomical label, cluster size (voxels), peak MNI coordinates, TFCE value and peak t-statistic. Results are corrected for multiple comparisons (5000 permutations).

Whole-brain main effect of task summary

In summary, the task reliably engaged fronto-striatal circuitry across both anticipation and outcome phases, with consistent activation of insula and thalamus in valence-related contrasts. This activation pattern is consistent with prior incentive and instrumental learning neuroimaging literature.

Region of Interest (ROI) main effect of task (all participants)

Given a priori hypotheses regarding striatal involvement in reward and loss processing during probabilistic instrumental learning, ROI analyses focused on the left and right dorsal striatum

and the left and right nucleus accumbens. ROIs were defined anatomically using an atlas-based mask, independent of the present data.

Anticipation phase

The win anticipation > baseline contrast showed significant activation in both the right dorsal striatum (t = 4.88, $p < 0.001$, peak voxel location: x =20, y =16, z = -2, cluster size = 361 voxels) and left dorsal striatum (t = 4.89, $p < 0.001$, peak voxel location: x = -28, y =-2, z = -4, cluster size = 694 voxels). Similarly, the loss anticipation > baseline contrast showed significant activation in both the right dorsal striatum (t = 4.47, $p < 0.001$, peak voxel location: x = 20, y = 12, z = -4, cluster size = 493 voxels) and the left dorsal striatum (t = 5.08, $p < 0.001$, peak voxel location: x = -22, y = 2, z = -6, cluster size = 773 voxels).

No significant activation was observed in either dorsal striatal ROI for the win anticipation > loss anticipation contrast. In contrast, the loss anticipation > win anticipation contrast showed significant activation in both the right dorsal striatum (t = 5.07, $p < 0.001$, peak voxel location: x = 14, y = 14, z = 2, cluster size = 89 voxels) and left dorsal striatum (t = 4.06, $p < 0.001$, peak voxel location: x = -12, y = 14, z = 14, cluster size = 86 voxels).

Outcome phase

The win outcome > baseline showed significant activation in both the right dorsal striatum (t = 5.56, $p < 0.001$, peak voxel location: x =14, y =8, z = -10, cluster size = 151 voxels) and left dorsal striatum (t =5.23, $p < 0.001$, peak voxel location: x =-14, y =8, z =-10, cluster size = 168 voxels. No significant activation was observed in any ROI for the loss outcome > baseline contrast.

The win outcome > loss outcome showed significant activation in both the right dorsal striatum (t =5.65, $p < 0.001$, peak voxel location: x =16, y = 8, z = -10, cluster size = 225 voxels) and left dorsal striatum (t = 5.87, $p < 0.001$, peak voxel location: x = -16, y = 6, z = -1, cluster size = 342 voxels). No significant activation was observed for the loss outcome > win outcome contrast.

The loss outcome > no loss outcome contrast showed significant activation in the right dorsal striatum activated (t = 4.21, $p < 0.001$, peak voxel location: x = 12, y = 4, z = 12, cluster size = 4 voxels). Conversely, the no-loss outcome > loss outcome contrast showed significant activation in both the right dorsal striatum (t =4.36, p < 0.001, peak voxel location: x = 12, y = 22, z = 2, cluster size voxels=24) and the left dorsal striatum (t =3.84, p =0.02, peak voxel location: x = -16, y = 10, z = -6, cluster size = 22 voxels).

The win outcome > no win outcome contrast showed significant in both the right dorsal striatum (t = 4.85 , p <0.001, peak voxel location: x = 18, y = 8, z = -12 , cluster size = 318 voxels) and (t = 4.02 , p = 0.02, peak voxel location: x = 14, y = -4, z = 18 , cluster size = 10 voxels) and the left dorsal striatum (t = 6.35 , p =<0.01, peak voxel location: x= -14, y = 6, z = -10 , cluster size = 246 voxels). No significant activation was observed for the no-win > win outcome contrast.

The nucleus accumbens ROI did not show significant activation in any contrast.

ROI main effect of task summary

Across anticipation and outcome phases of the task, dorsal striatal ROIs showed robust task-related activation, consistent with their established role in instrumental learning. Although whole-brain analyses identified significant activation within the nucleus accumbens, ROI-based analyses did not show significant activation in the nucleus accumbens ROI in any contrast.

Whole Brain

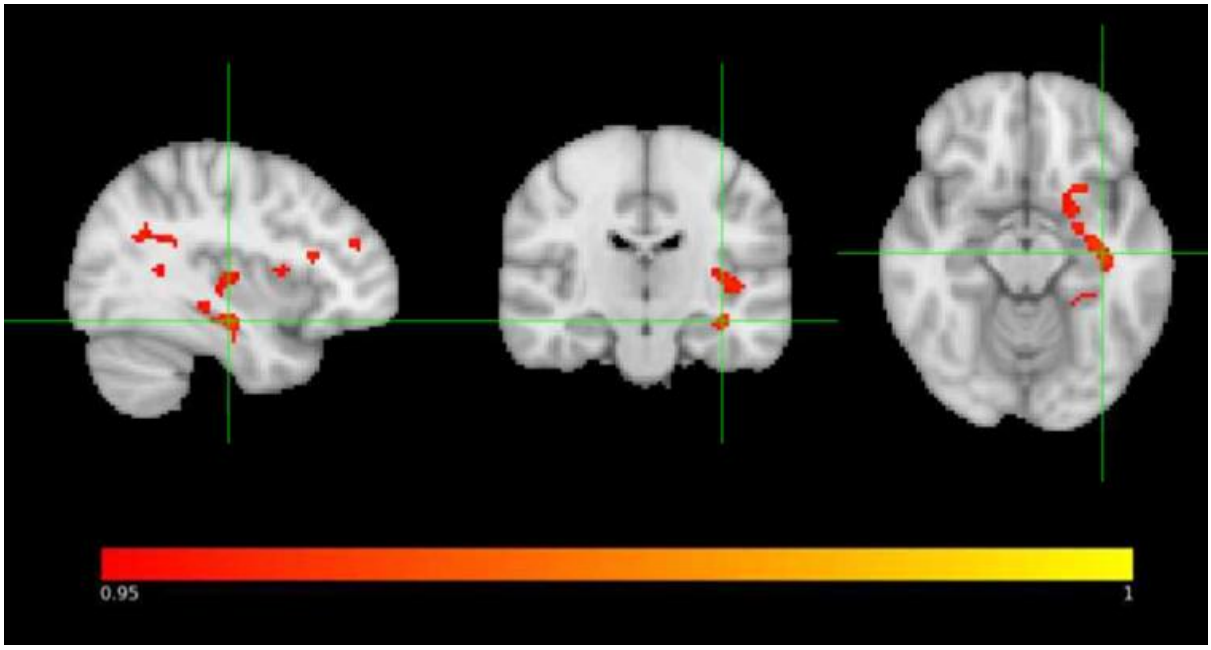
Effects of ketamine / group differences for anticipation phase

No significant group differences were observed during the anticipation phase for either win or loss trials.

Effects of ketamine / group differences for outcome phases

When comparing ketamine to placebo, there was a significant differential activation for win outcome vs loss outcome in 23 clusters (**Figure 5.10**). The largest cluster encompassed regions within the left hippocampus, amygdala, orbitofrontal cortex, putamen, and parahippocampal gyrus ($t = 4.41$, $p = 0.04$, peak voxel location: x = -36, y = -18, z = -14, cluster size = 371 voxels). Additional significant clusters were observed in the anterior cingulate and paracingulate cortices, caudate nucleus, middle frontal gyrus ($t = 3.86$, $p = 0.04$, peak voxel location: x = 24, y = 24, z = 8, cluster size = 338 voxels, insula ($t = 3.86$, $p = 0.04$, peak voxel location: x = -30, y = −38, z = -10, cluster size = 334 voxels) and thalamus ($t = 4.19$, $p = 0.04$, peak voxel location: x = -16, y = −12, z = 6, cluster size = 102 voxels). Across these regions, the ketamine group showed greater neural responses to win outcomes alongside reduced responses to loss outcomes. Full details of all significant clusters are provided in **Table A1 (Appendix)**.

A)



B)

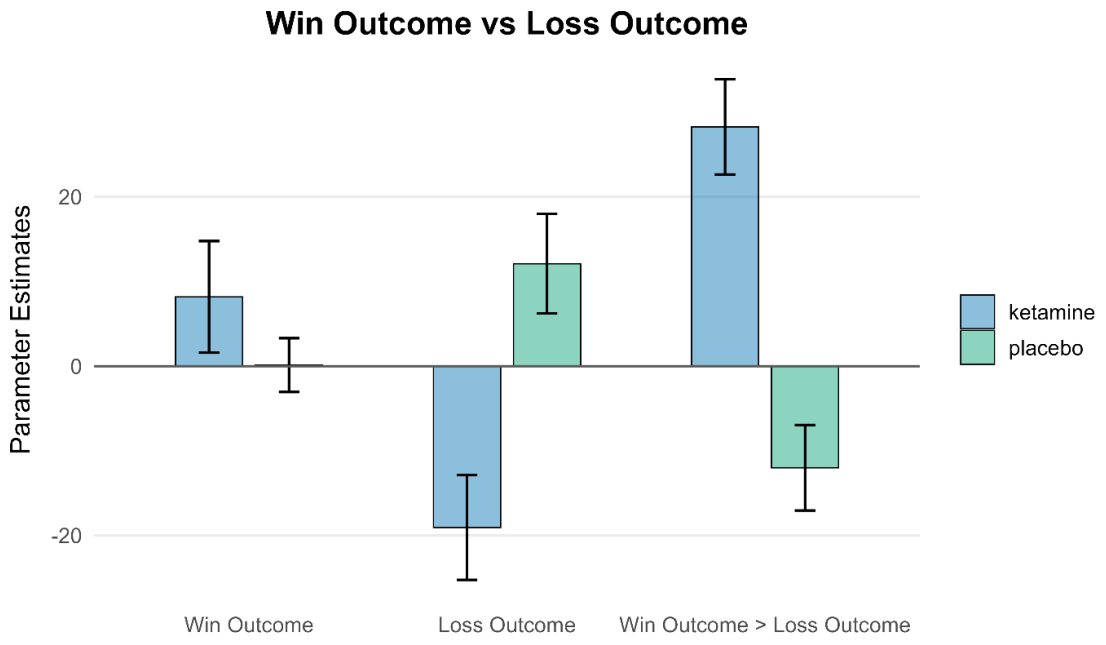
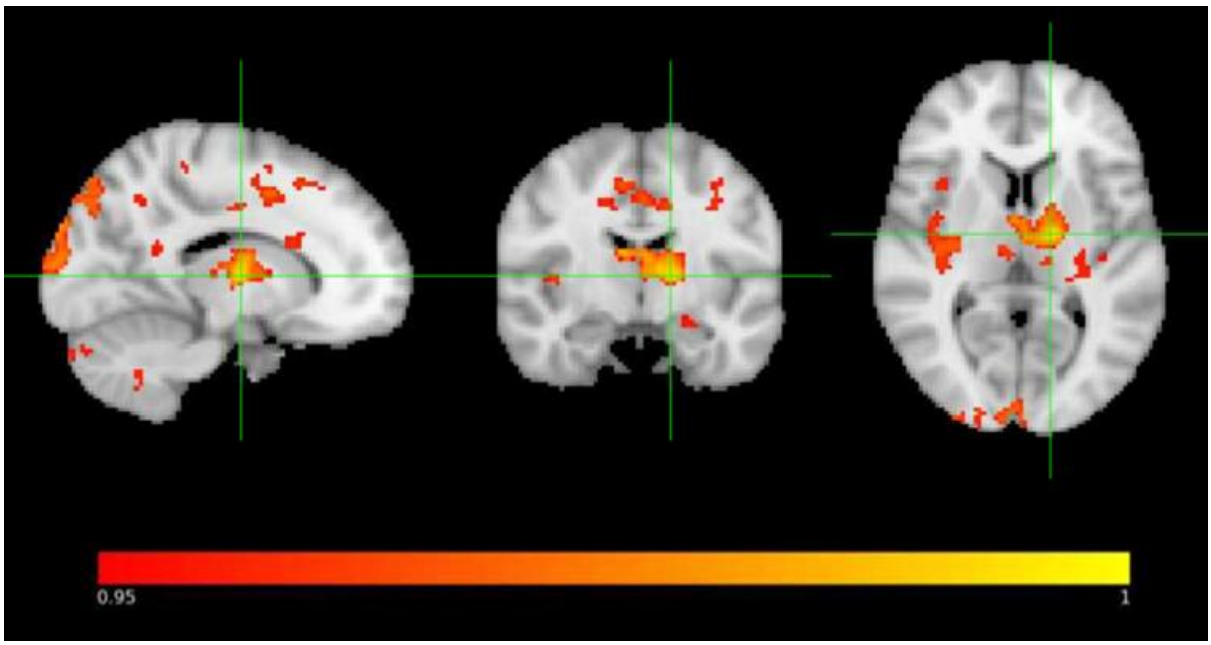


Figure 5.10. Effect of ketamine compared to placebo on whole brain activation win outcome vs loss outcome. Panel A displays the whole-brain contrast between ketamine and placebo for the win outcome relative to loss outcome comparison, thresholded using TFCE at $p < 0.05$, FWE-corrected (5,000 permutations). The cursor is located in the left hippocampus (MNI coordinates: [x = -36, y =-18, z = -14]). **Panel B** shows parameter estimates extracted from all

significant clusters identified in the win outcome > loss outcome contrast. To examine the direction of the effect, parameter estimates for win and loss outcomes were extracted separately using the same mask. Error bars represent the standard error of the mean.

In contrast, loss outcomes relative to no-loss outcomes showed significantly greater activation in the placebo group when compared to ketamine **(Figure 5.11**) across overlapping cortico-striato-limbic regions such as the thalamus including cingulate gyrus posterior, caudate (t = 6.05, p = 0.01, peak voxel location: x = -14, y = −10, z = -6, cluster size = 1239 voxels), cingulate gyrus anterior, precentral gyrus, superior frontal gyrus, paracingulate gyrus (t = 4.41, p = 0.01, peak voxel location: x = 4, y =0, z = 40, cluster size = 1051 voxels), putamen including insular (t = 4.19, p = 0.01, peak voxel location: x = 30, y = −16, z = 8, cluster size = 248 voxels), with the largest cluster in the occipital cortex including the precuneus gyrus (t = 3.65, p = 0.01, peak voxel location: x = -28, y = -96, z = 16, cluster size = 1785 voxels). Full details of all significant clusters are provided in **Table A2 (Appendix**).

A)



B)

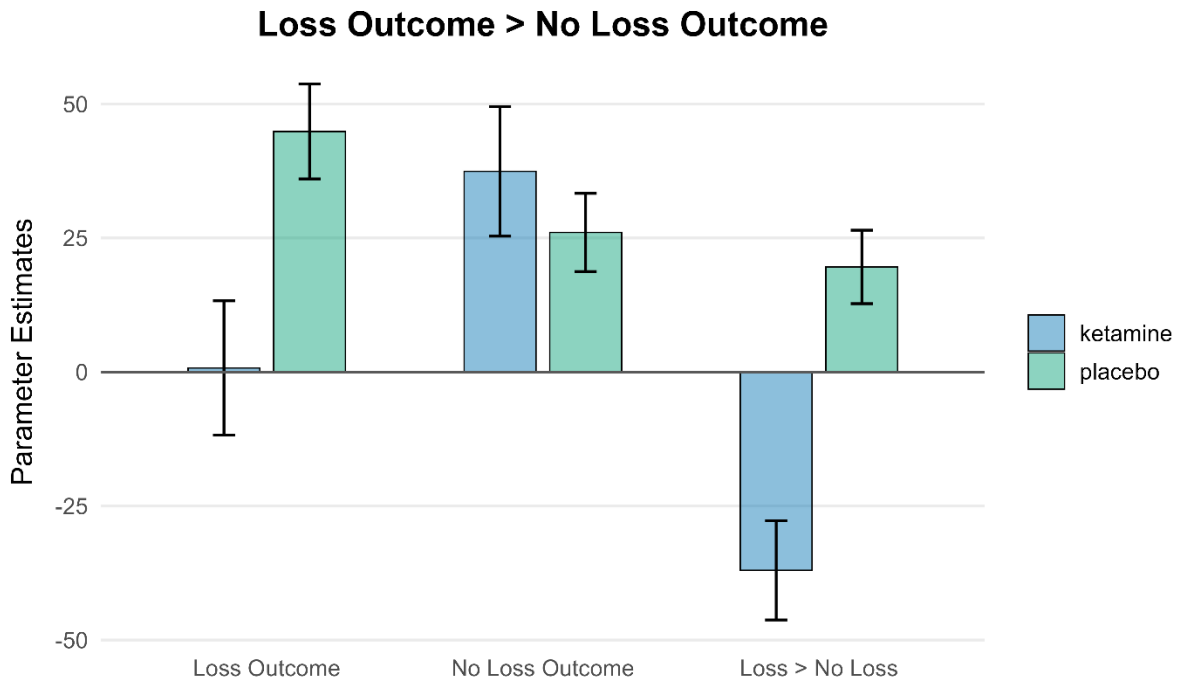


Figure 5.11. Effect of ketamine compared to placebo on whole brain activation loss outcome > no loss outcome. Panel A displays whole-brain difference between ketamine and placebo for the loss outcome > no loss outcome, thresholded using TFCE at $p < 0.05$ FWE-corrected (5000 permutations). Cursor located in the left thalamus, (MNI coordinates: [x = -14, y = -10, z = 6]). **Panel B** shows parameter estimates extracted from all significant clusters for the loss outcome > no loss outcome contrast. To examine the direction of the effect, parameter estimates for win and loss outcomes were extracted separately using the same mask. Error bars represent the standard error of the mean.

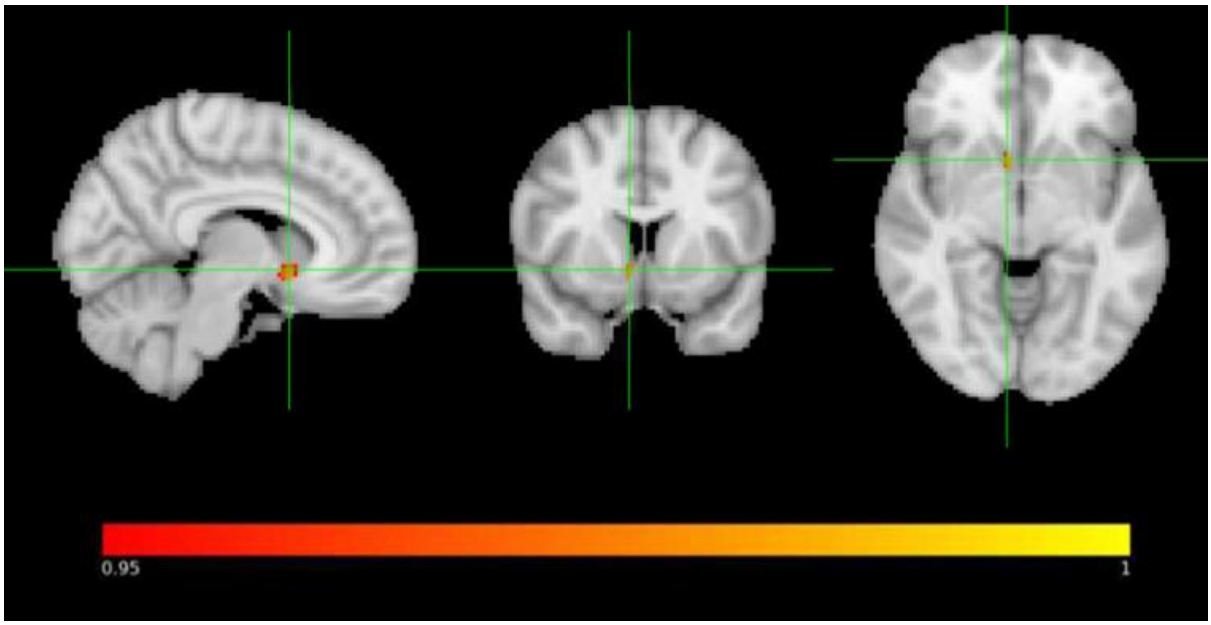
Region-of-Interest Analysis

Striatum

Nucleus accumbens

In the right nucleus accumbens, loss outcome relative to baseline (fixation cross) was associated with deactivation, which was significantly greater under ketamine compared with placebo (29 voxels, peak MNI voxel location: x= 6, y = 12, z = -6; **Figure 5.12**).

A)



B)

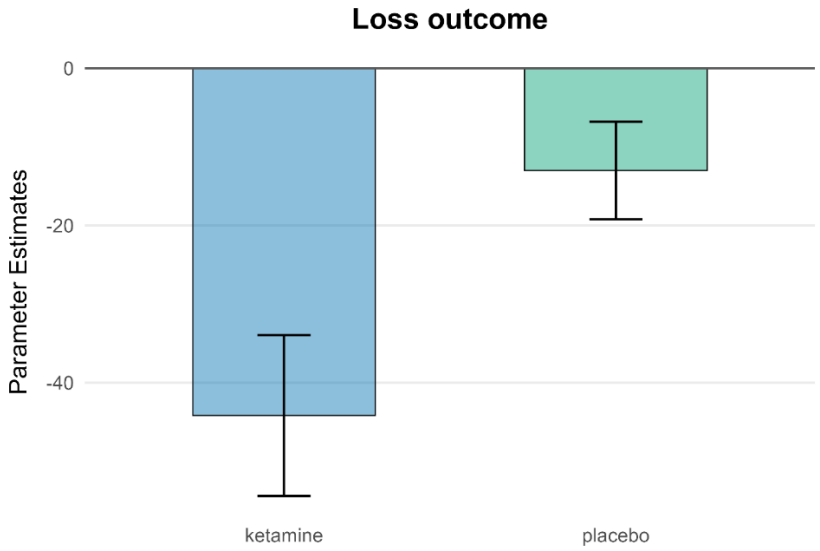
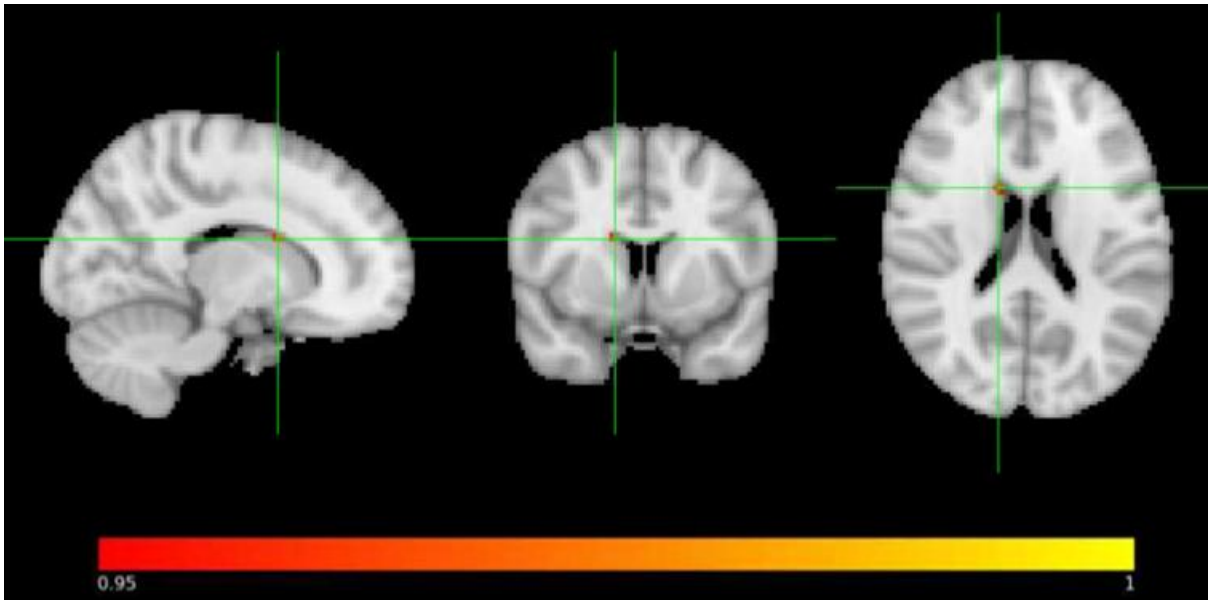


Figure 5.12. Ketamine group have significantly reduced activation when responding to loss vs baseline. Panel A. Statistical map shows differences within the anatomically defined right nucleus accumbens ROI for the loss outcome > baseline contrast, thresholded using TFCE at $p < 0.05$, FWE-corrected (5,000 permutations). MNI coordinates: [x = 6, y = 12, z = -6]. **Panel B.** Mean parameter estimates extracted from the right nucleus accumbens ROI for the loss outcome > baseline contrast. Error bars represent the standard error of the mean.

Right Dorsal Striatum ROI

The ketamine group showed significantly reduced activation in the caudate when receiving a loss vs no loss when compared to placebo group (8 voxels, peak MNI voxel location: x = 14, y = 8, z = 20 $p = 0.04$; **Figure 5.13**).

A)



B)

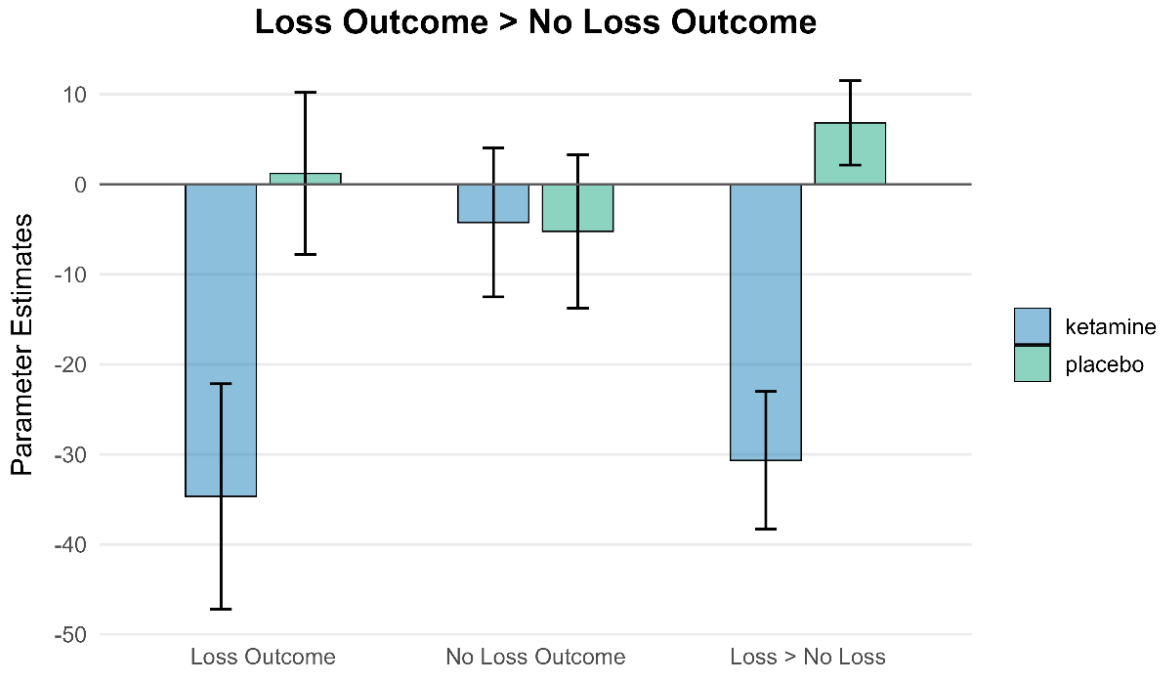
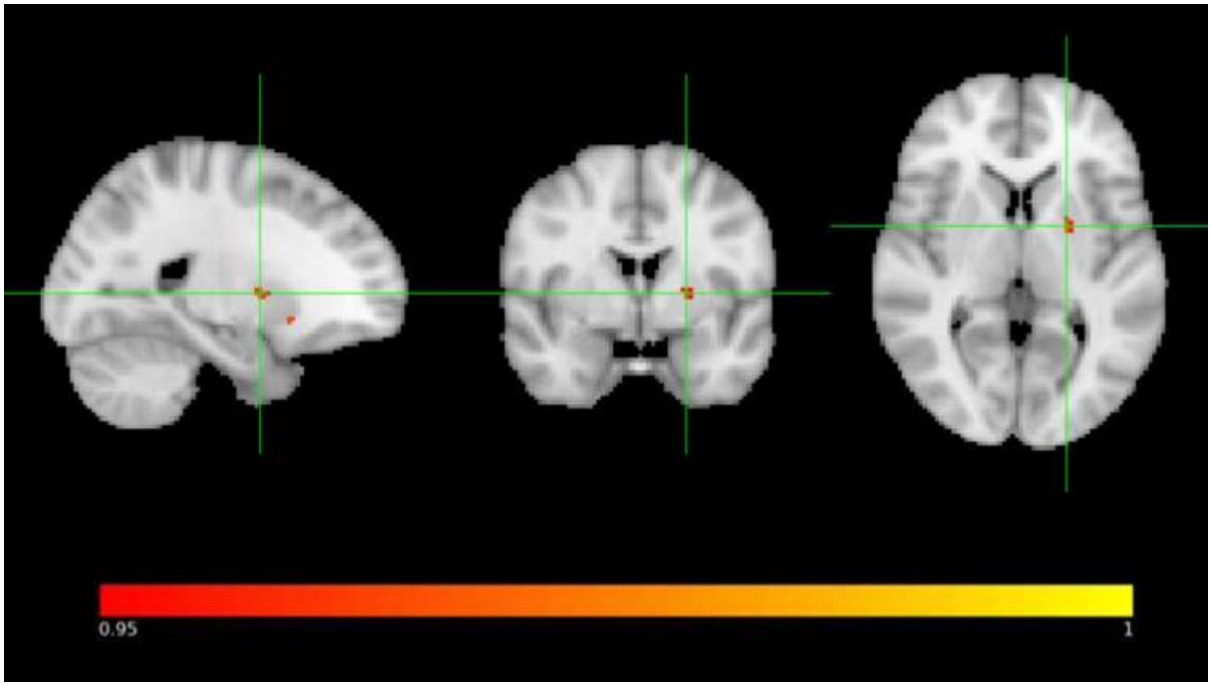


Figure 5.13. Ketamine group have significantly reduced activation when receiving a loss vs no loss in the caudate. Panel A. Statistical map shows differences within the anatomically defined right dorsal striatum ROI for the loss outcome > no loss contrast, thresholded using TFCE at $p < 0.05$, FWE-corrected (5,000 permutations). MNI coordinates: [x = 14, y = 8, z = 20]. **Panel B.** Mean parameter estimates extracted from the right dorsal striatum ROI for the loss outcome > baseline contrast. Error bars represent the standard error of the mean.

Left Dorsal Striatum ROI

The ketamine group showed significantly greater activation in the putamen (21 voxels, peak MNI voxel location: x=-22, y=0, z=4, p=0.03, 7 voxels, peak MNI voxel location: x = -22, y = 14, z = -10, p = 0.04 and 1 voxel, peak MNI voxel location: x = -30, y = -14, z = 8, p = 0.05) when receiving a win when compared to when receiving a loss and compared to placebo group (**Figure 5.14**).

A)



B)

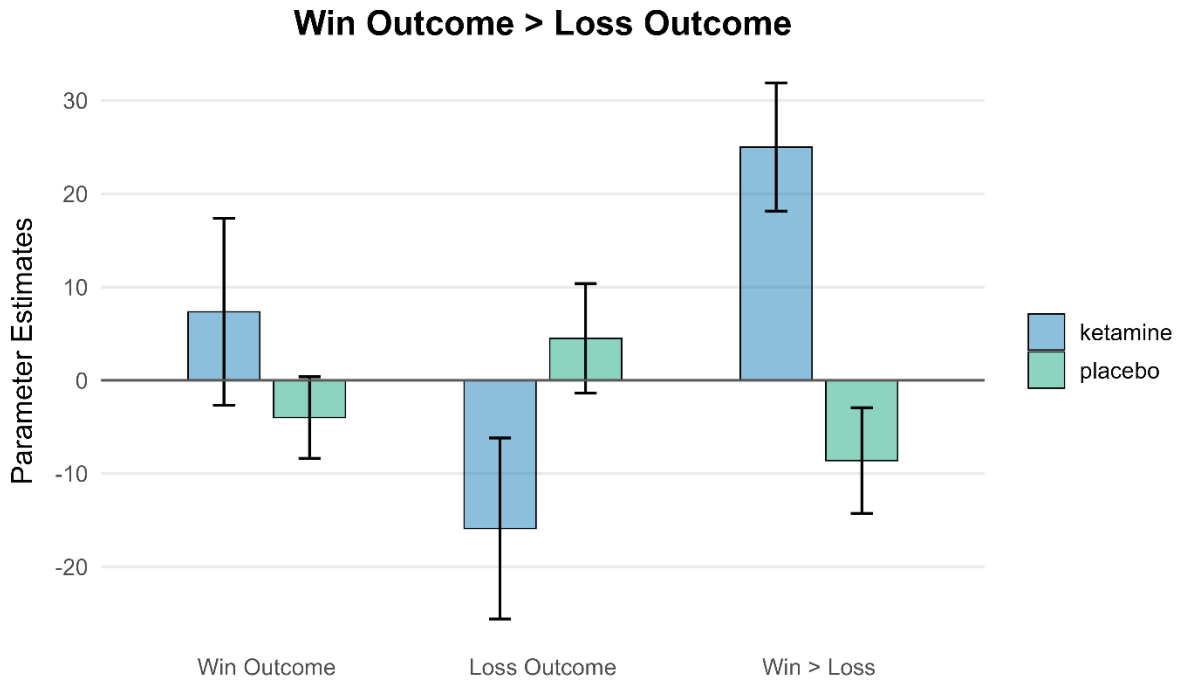


Figure 5.14. Ketamine group have significantly increased activation when receiving a win vs a loss in the left putamen. Panel A. Statistical map shows differences within the anatomically defined left dorsal striatum ROI for the win outcome > loss contrast, thresholded using TFCE at $p < 0.05$, FWE-corrected (5,000 permutations). The cursor is located in MNI coordinates: [x = -

22, y = 0, z = 4]). **Panel B.** Mean parameter estimates extracted from the left dorsal striatum ROI for the loss outcome > baseline contrast. Error bars represent the standard error of the mean.

Model based analysis

Model-derived prediction errors were entered as parametric modulators at feedback onset. The ketamine group showed a trend-level increase in loss prediction error tracking in the nucleus accumbens relative to placebo (20 voxels, peak MNI voxel location: x = 8, y = 10, z = -10, p = 0.07); however, this effect did not reach statistical significance. Similarly, trend-level increases in loss prediction error tracking were observed in the dorsal striatum, in both the left (2 voxels, peak MNI voxel location: x = -28, y = -22, z = 6, p = 0.06) and right (2 voxels, peak MNI voxel location: x=30, y = -18, z = 8, p = 0.08) hemispheres under ketamine compared with placebo, though these effects did not survive family-wise error correction at $p < 0.05$. No significant group differences were observed for win prediction error encoding in either ventral or dorsal striatum.

In contrast, a significant group difference was observed in the insula for the loss trial prediction error regressor, with greater BOLD coupling in the ketamine group compared with placebo (36 voxels, peak MNI voxel location: x = 42, y = -6, z = 4, p = 0.02; **Figure 5.15**).

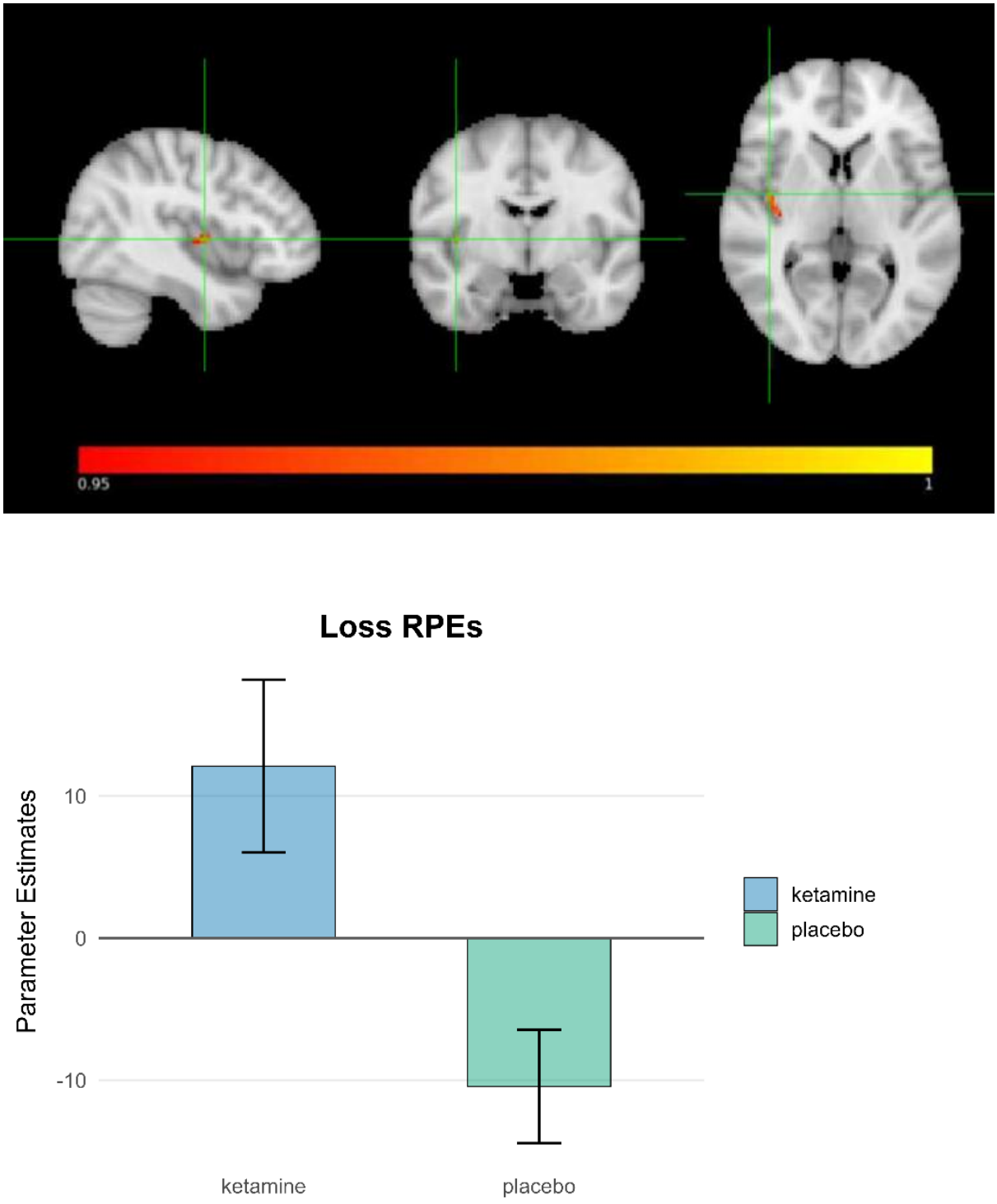


Figure 5.15. ROI insula showing greater coupling under ketamine relative to placebo. Panel A. Statistical map shows the bilateral ROI insula for loss RPEs, thresholded using TFCE at $p < 0.05$. MNI coordinates [x = 42, y = -6, z = 4]. **Panel B.** Parameter estimates from the loss trials prediction error regressor extracted from ROI insula, showing greater coupling under

ketamine relative to placebo. Positive values indicate stronger neural sensitivity to better-than-expected outcomes in the loss condition (no-loss/avoidance).

Discussion

The present study investigated the effects of ketamine, assessed one day following infusion, on neural responses to wins and losses during a probabilistic instrumental learning task (PILT) in medicated individuals with treatment-resistant depression. Behavioural, neuroimaging, and computational modelling approaches were used to examine these effects at both the whole-brain level and within predefined striatal and insular regions of interest.

Overall, the findings indicate that ketamine increases neural differentiation between rewarding and loss outcomes. Specifically, ketamine was associated with reduced neural responses to loss outcomes, alongside increased responses to wins and to unexpected no loss in aversive contexts, (e.g., avoidance of monetary loss). Ketamine was also associated with significantly greater coupling between loss-condition prediction errors and anterior insula activity. Notably, these effects were observed in the absence of behavioural change, suggesting early modulation of neural computations that may precede measurable changes in performance or clinical symptoms.

Task engagement and absence of behavioural effects

Across both groups, the PILT reliably engaged regions implicated in reward and loss processing, including prefrontal, limbic and insular cortices (Wilson et al., 2018). Anticipatory activation was observed primarily within frontal, insular and dorsal striatal regions, while ventral striatal engagement did not survive correction for multiple comparisons. This pattern is consistent with the instrumental and action-contingent nature of the task, which preferentially recruits dorsal striatal circuitry for action-outcome learning.

No significant group differences were observed in behavioural performance or in reinforcement learning parameters, including learning rate and inverse temperature, estimated separately for win and loss trials. Despite this, ketamine was associated with distinct alterations in outcome-related and learning-related neural signals. This pattern is consistent with previous findings that ketamine may exert subacute effects on neural processing mechanisms that are not immediately observed behaviourally (Kotoula et al., 2022). The present findings may therefore reflect a latent recalibration of affective learning systems that is not yet apparent at the behavioural level one day after infusion.

Ketamine and anticipatory processing

No significant group differences were observed during the anticipation phase for either win or loss trials. This finding is consistent with evidence suggesting that ketamine's effects on reward processing are more prominent during the outcome stage. For example, Kotoula et al. (2022) reported increased activation in reward-related regions during reward anticipation following ketamine administration. However, these previously reported effects were weaker than those observed during reward receipt. Notably, that study did not include medicated individuals with depression. Other work similarly suggests that ketamine modulates reward circuitry during the feedback phase, with anticipatory effects being less robust and largely confined to reward rather than loss conditions (Morris et al., 2020).

One interpretation of the absence of anticipatory effects in the present study relates to the mechanisms supporting reward anticipation. Anticipatory processing relies heavily on dopaminergic signalling involved in prediction and incentive salience, shaping expectations about future outcomes rather than responses to outcomes once they occur. Evidence that antidepressant-related changes in monoaminergic systems reliably normalise these prediction-related processes

remains limited and inconsistent, particularly in treatment-resistant depression (Lan & Browning, 2022). Within this study, where both the ketamine and placebo groups were taking conventional antidepressants, anticipatory reward signalling may be relatively resistant to acute pharmacological modulation, thereby limiting detectable group differences during the anticipation phase.

Ketamine increases neural differentiation between win and losses

In contrast to the absence of anticipatory effects, ketamine was associated with increased BOLD activation during the outcome phase. Whole-brain analyses revealed that the ketamine group showed significantly greater differentiation between win and loss outcomes relative to the placebo group. This effect was observed across a limbic-striatal-prefrontal network, including the amygdala, hippocampus, orbitofrontal cortex, putamen, anterior cingulate cortex, caudate, insula, and thalamus. Across these regions, ketamine was characterised by increased responses to rewarding outcomes alongside attenuated responses to losses. These findings indicate that ketamine enhances the neural distinction between win and loss outcomes during outcome processing.

Putamen involvement in reward learning

Consistent with the study predictions, increased activation was observed in the putamen in the ketamine group during win outcomes relative to loss outcomes compared with the placebo group. The putamen has been implicated in reward-processing abnormalities in depression, with prior work reporting reduced striatal responses to rewarding outcomes in individuals with depression (Pizzagalli et al., 2008). In the present study, this effect was found both in the whole-brain analysis and within a left dorsal striatal region of interest, highlighting the robustness of the finding. The putamen plays a central role in reinforcement-driven action selection and outcome-based learning, processes that are directly engaged by the probabilistic instrumental learning task. Increased win-

loss differentiation in this region therefore suggests a sharpening of outcome representations relevant for updating action values, rather than a general increase in reward responsivity.

Previous work by Kotoula et al. (2022) similarly reported increased nucleus accumbens and putamen activation following ketamine administration during reward processing. Although that study used a monetary incentive delay task rather than an instrumental learning paradigm, and did not include loss trials or individuals with depression, both tasks engage striatal circuitry during outcome evaluation. The convergence of findings therefore supports the involvement of striatal reward circuitry in ketamine's effects across distinct reward-processing contexts. Importantly, in individuals with treatment-resistant depression, where reward feedback often fails to effectively guide behaviour, enhanced differentiation between rewarding and aversive outcomes within the putamen may reflect a mechanism through which ketamine biases reinforcement learning toward positive feedback.

In addition to striatal effects, increased activation was observed within medial temporal and limbic regions implicated in affective outcome valuation.

Amygdala and medial temporal involvement in outcome processing

Although the amygdala was not a predefined region of interest, its involvement is consistent with evidence identifying it as a key cortico-limbic structure showing abnormal activity to emotionally salient stimuli in major depressive disorder (Cheng et al., 2018; Perlman et al., 2019; Tang et al., 2018). Beyond its role in emotional regulation, the amygdala is critically involved in reinforcement learning, encoding motivational salience for both positive and negative outcomes and interacting with striatal and prefrontal regions during outcome processing and value updating (Delgado et al., 2008; Hampton et al., 2007; Murray, 2007). During associative learning, amygdala-cortical

interactions are shaped by inputs from hippocampal and orbitofrontal regions (Kringelbach, 2004), both of which were included within the observed outcome-related cluster. Neuroimaging studies further indicate that amygdala activity differentiates winning from losing feedback and interacts with striatal regions during outcome evaluation and value updating ((Delgado et al., 2008; Watanabe et al., 2013).

In the present study, ketamine was associated with increased activation in the amygdala during win outcomes alongside reduced responses during loss outcomes. This pattern may reflect a selective, valence-specific shift in outcome valuation rather than a generalised increase in emotional reactivity. This interpretation is consistent with prior ketamine research showing reduced amygdala reactivity to negatively valanced affective stimuli (Scheidegger et al., 2016). Although that study used emotional face stimuli in healthy participants, it supports the present findings by showing attenuation of negative salience processing. The current study extends this work by showing similar effects within an instrumental learning task in a clinical population with treatment-resistant depression.

Importantly, these ketamine effects were observed in participants receiving ongoing antidepressant treatment. Conventional antidepressants are often associated with reduced amygdala reactivity to aversive stimuli (Fitzgerald et al., 2008; Godlewska et al., 2012) but limited improvement in reward processing. The presence of increased win-related activation and reduced loss-related activation under ketamine is therefore consistent with engagement of outcome valuation processes beyond those typically modulated by standard antidepressant treatment. In contrast, the placebo group showed greater loss-related activation and reduced win-related activation, consistent with established patterns of negative bias and blunted reward responsivity in depression (Eshel & Roiser, 2010; Pizzagalli et al., 2008).

Increased activation in the loss outcome vs no loss outcome for placebo group

Whole-brain analyses showed a significantly greater activation in the placebo group during loss outcomes compared with no-loss outcomes across cortico-striato-limbic regions, including the thalamus, caudate, putamen, insula and occipital cortex. These findings are consistent with prior reports of heightened sensitivity to negative outcomes in depression and support the notion of exaggerated punishment-related neural responses in individuals with persistent or treatment-resistant symptoms.

This effect was also evident in the right dorsal striatal region of interest, with greater activation in the right caudate for loss outcomes relative to no-loss outcomes in the placebo group compared with ketamine. Previous work has suggested that ketamine may modulate altered caudate responses in treatment-resistant depression, with changes in caudate-prefrontal resting-state connectivity observed following treatment and associated with clinical response (Mkrtchian et al., 2021).

In addition, the nucleus accumbens region of interest showed greater loss-related activation in the placebo group relative to ketamine. Although this contrast reflected loss outcomes relative to baseline rather than no-loss outcomes, the convergence of whole-brain and ROI findings supports the interpretation of reduced loss signalling within striatal circuitry following ketamine.

Ketamine and salience modulation

Building on the loss-related effects described above. Ketamine was associated with a shift in neural responses within cortico-striato-limbic regions implicated in salience processing including the insula, thalamus, caudate and putamen. Rather than reflecting a general dampening of processing, this pattern may suggest reduced sensitivity to aversive outcomes (loss) alongside enhanced processing of safety/relief (no loss).

Ketamine has been shown to modulate insular connectivity in depression, including normalisation of interactions between the salience network and default mode network following treatment (Evans et al., 2018). Improvements in depressive symptoms one day post-infusion have also been associated with changes in insular and default mode network activity (Abdallah et al., 2017). These findings support the interpretation that ketamine may recalibrate salience processing, increasing sensitivity to non-aversive outcomes in contexts where negative bias is typically more pronounced.

Clinically, this result may reflect a shift in the processing of affective information, with reduced weighting of negative outcomes and greater sensitivity to signals of safety or potential reward in individuals with treatment-resistant depression.

Prediction error signalling and loss learning

To probe the computational mechanisms underlying these outcome-related effects, model-based analyses focused on prediction error signalling. Model-based fMRI analyses revealed no significant group differences in striatal prediction error signalling for win outcomes and only trend-level effects for loss-condition prediction errors. Behavioural analyses similarly showed non-significant trends toward faster updating following rewarding outcomes and increased avoidance of loss under ketamine. The absence of robust striatal prediction error effects contrasts with some prior reports in depression (Kumar et al., 2008) and may reflect limited statistical power, modest trial numbers per valence, or the influence of concurrent antidepressant treatment, as discussed above.

In contrast, ketamine was associated with significantly greater coupling between loss-condition prediction errors and anterior insula activity. Loss prediction errors were sign-coded such that positive values reflected better-than-expected outcomes corresponding to avoidance of loss.

Enhanced insula tracking of these signals under ketamine therefore suggests increased sensitivity to unexpected relief or omission of negative outcomes, rather than heightened punishment processing per se. The anterior insula plays a central role in the salience network and has been consistently implicated in aversive learning, interoceptive processing, and the encoding of prediction-error-like signals, particularly in contexts involving uncertainty or threat (Haruno & Kawato, 2006; Jones et al., 2011).

Ketamine has been proposed to alter belief updating by modifying the precision-weighting of prediction errors in affective contexts characterised by rigid negative priors, that is, strongly held expectations of negative outcomes that are resistant to updating even when experiences are better than expected (Adams et al., 2013; Corlett et al., 2016; Sterzer et al., 2018). In the present study, enhanced insula coupling to positive loss-domain prediction errors under ketamine may therefore reflect increased learning from unexpected relief or safety signals that are otherwise underweighted in depression. Computationally, this pattern supports complementary roles for insular and striatal regions, whereby the insula encodes salience-based updating while striatal circuits support action selection and avoidance learning (Frank, 2005; Haber & Knutson, 2010; Menon & Uddin, 2010; O'Doherty et al., 2004; Palminteri et al., 2012).

Overall, the results suggest that ketamine shifts the neural weighting of outcome information, with reduced weighting of negative outcomes and increased sensitivity to unexpected relief, consistent with altered salience and belief updating in treatment-resistant depression.

Strengths, limitations, and future directions

Several limitations should be considered when interpreting these findings. All participants were receiving ongoing antidepressant medication, which is known to attenuated behavioural and neural

sensitivity to reward and punishment and introduced heterogeneity in reinforcement learning signals (Kumar et al., 2008; Lawson et al., 2017; McCabe et al., 2010). This may have contributed to the absence of anticipatory effects observed in the present study and warrants further investigation in future work. A strength of including participants receiving antidepressant treatment is that it reflects real-world ketamine administration in treatment-resistant depression and enhances the generalisability of the findings. Importantly, the study found a significant outcome-related neural effect despite concomitant antidepressant treatment, suggesting that ketamine may exert effects on outcome processing that extend beyond those typically modulated by conventional antidepressants.

Although between-group differences were observed at the outcome stage, it would have been beneficial to include a baseline fMRI scan to assess within-subject changes in neural activation before and after ketamine administration. However, the study involved a complex and demanding protocol in a treatment-resistant population, including five study visits. The addition of a further scanning session may have increased participant burden and reduced overall data quality.

Head motion was a concern in a subset of participants, although standard correction procedures were applied. Residual motion effects may disproportionately affect fronto-striatal regions. The observation of group differences within white matter regions may similarly reflect residual motion-related artefacts rather than task-related neural activity. Analyses were repeated using a grey matter mask, and the main findings remained significant, suggesting that the observed effects were not driven solely by signal outside grey matter. Nevertheless, caution is warranted when interpreting apparent white matter activations in fMRI data. Structural imaging studies have reported abnormalities in mesolimbic white matter tracts implicated in reward processing in depression (Bracht et al., 2015), highlighting the relevance of white matter pathways to affective learning.

Further research also suggests that grey matter volumetric changes may be associated with reward processing (Abdallah et al., 2018).

Conclusion

In conclusion, the present findings indicate that ketamine is associated with altered neural processing of reward and loss in treatment-resistant depression. Specifically, attenuated neural sensitivity to negative outcomes and enhanced differentiation of rewarding outcomes during outcome evaluation and learning. These effects were observed within dorsal striatal, cortico-striato-limbic, and salience-related circuits and in the absence of immediate behavioural change. The results are consistent with models proposing glutamate-dependent plasticity and altered precision-weighting of prediction errors.

Overall, these results contribute to a more mechanistic understanding of how ketamine may modulate affective learning systems in depression. The study also highlights the importance of using neuroimaging, computational modelling, and psychopharmacological approaches in the study of antidepressant effects. This approach is particularly important given the clinical complexity and heterogeneity of depression, where persistent alterations in reward and loss processing can profoundly shape motivation, decision-making, and everyday functioning in individuals who have not responded to conventional treatments.

Chapter 6: The effects of ketamine on effort-based decision making in treatment-resistant depression

Introduction

Reward processing involves several related components, including reinforcement learning, reward valuation, reward responsiveness and motivation or effort-based decision making. Alterations in any of these components can contribute to anhedonia, a core feature of major depressive disorder (MDD). As a result, many people with MDD struggle to re-engage in everyday activities even when other symptoms have improved. While the previous chapter focused primarily on reinforcement learning and reward responsiveness, this chapter focuses on motivation, specifically how individuals decide whether exerting effort is "worth it" to obtain a reward, and how this might be modulated by ketamine in treatment-resistant depression (TRD).

Many everyday choices require a balance between the expected value of an outcome and the effort needed to obtain it. For some people, getting out of bed, going to work, meeting a friend or engaging in a hobby feels relatively automatic. For others, particularly those with depression, these actions involve deliberate cost-benefit evaluation: *do I have the energy for this, and is it worth it?* This evaluation can be especially difficult when effort feels overwhelming even for activities that are valued, or when there is willingness to exert effort, but the anticipated reward no longer feels meaningful. Obtaining rewards therefore requires both perceiving the outcome as rewarding and being willing to invest physical and/or cognitive effort. In depression, one or both of these processes can be impaired, often alongside symptoms such as apathy and fatigue which leads to cognitive and motivational deficits that interfere with daily functioning and recovery. However, it remains unclear to what extent people with depression show specific deficits in balancing effort against reward, as opposed to broader impairments in reward or effort sensitivity.

These processes can be studied with effort-based decision-making tasks. The Effort Expenditure for Reward Task (EEfRT) is a common paradigm that assesses choices between an easy low-reward option and a more effortful option associated with higher and probabilistic rewards (Treadway et al., 2009). Studies using this task have found that individuals with higher levels of depression or anhedonia are less willing than healthy individuals to select high-effort/high-reward options (Tran et al., 2021; Treadway et al., 2009, 2012; Yang et al., 2014). Greater self-reported anhedonia has been associated with reduced willingness to expend effort for larger rewards suggesting that motivational impairments are an important component of anhedonia that requires further investigation (Treadway et al., 2009; Treadway & Zald, 2011). However, there are some inconsistencies with some studies finding no clear differences (Culbreth et al., 2024). This could reflect heterogeneity within depression and other factors such as comorbidities, symptom severity and medication status. Although the EEfRT has advanced our understanding of effort-based decision making in depression, it has its limitations. For example, disentangling reward and effort parameters can be difficult using this paradigm, and the repeated button-pressing response as a proxy for effort may lack ecologically validity. These limitations have motivated the development of alternative tasks that can better separate effort and reward parameters, and more closely resemble everyday motivational choices.

One such task is the Apple Gathering Task, developed to model effort and reward-based decision making in a more ecologically valid way (Bonnelle et al., 2015). In this task, participants are presented with offers that vary in reward and effort levels. Effort is exerted using a physical grip-force device calibrated to each participant's maximum voluntary contraction, rather than repeated button pressing. During the offer phase, participants decide whether to accept or reject each offer based on whether they consider the reward worth the required effort. In a subsequent work phase, a subset of accepted offers is randomly selected, and participants must exert the required grip force to obtain the associated reward.

A key strength of the AGT is that it enables reward and effort parameters to be modelled independently, allowing identification of whether motivational impairments arise from reduced reward sensitivity, increased effort cost sensitivity, or a combination of both. Studies using this task have shown that healthy individuals tend to accept high-reward/high-effort offers, whereas individuals with depression and other disorders with anhedonia accept fewer high-reward/high-effort offers and often show increased apathy (Saleh et al., 2023; Valton et al., 2025). In Parkinson's disease, where apathy and depression are highly prevalent, differences in reward-effort choice behaviour are strongly linked to apathy, highlighting the transdiagnostic relevance of these mechanisms (Costello et al., 2025; Husain & Roiser, 2018). Although apathy and anhedonia frequently co-occur in depression, they represent distinct constructs, studying both symptoms is therefore essential when studying reward processing.

As previously described, ketamine has been associated with changes in fronto-striatal functional connectivity, a key network for reward and motivation. Preclinical studies have also shown that sub-anaesthetic ketamine can alter the incentive-motivational value of reward-related cues (Fitzpatrick & Morrow, 2017) and rescue stress-induced synaptic deficits in nucleus accumbens medium spiny neurons (Lucantonio et al., 2025). Although ketamine appears to reduce anhedonia and modulate reward circuitry, very little work has examined its effects on effort-based decision making specifically. Most human studies use subjective anhedonia ratings or reward responsiveness tasks with relatively few using tasks that involve effort and reward.

Ketamine is known for its rapid antidepressant effects, but the timing of glutamatergic and dopaminergic action is not yet fully understood. Although peak antidepressant responses typically occur 24-72 hours post-infusion, preclinical and experimental studies indicate that some neural and behaviour changes can arise much earlier. Preclinical studies show that ketamine produces a

rapid and transient increase in glutamate release in medial prefrontal cortex, accompanied by increased dopamine in cortical and striatal regions within the first hour after administration (Kokkinou et al., 2018; Moghaddam et al., 1997). In humans, magnetic resonance spectroscopy (MRS) studies show indirect evidence of early glutamatergic changes after ketamine, including signs of increased prefrontal glutamate - glutamine cycling shortly after infusion (Abdallah et al., 2018; Kang et al., 2022). These findings raise the possibility that motivational processes could begin to shift early after ketamine, at least in animal models. However, the timing of such changes in humans is unknown. For this reason, the early preclinical window where glutamatergic and dopaminergic changes occur within the first hour, provided a reasonable window at which to investigate whether effort-reward decision making might also show early modulation after ketamine in humans.

To summarise, current evidence suggests that (1) motivational and effort-based components of reward processing are altered in individuals with depression; (2) tasks such as the Apples Gathering Task provide a useful framework for characterising these impairments; and (3) ketamine appears to produce rapid effects on anhedonia and reward-related neural circuits, but its impact on effort-based decision-making, particularly in treatment-resistant depression (TRD), remains poorly understood.

The present study aimed to investigate the effects of ketamine on effort-based decision-making in individuals with treatment-resistant depression using the Apples Gathering Task. Ketamine may influence effort-based decision-making not only at later antidepressant time points but also during the early period following infusion, when glutamatergic and dopaminergic changes are observed. To capture both acute and delayed effects, behaviour was assessed at two time points: an acute post-infusion assessment approximately 30 minutes after administration (T1), and a follow-up assessment one week later (T2). This design allowed us to test whether changes in effort-based decision-making emerged rapidly, persisted over time, or evolved across time points.

Chapter Aims and Hypotheses

This study aimed to investigate the acute and delayed effects of ketamine on motivation, specifically for rewards and how much effort people are willing to exert to obtain the reward.

Aim 1: To investigate whether ketamine alters reward and effort sensitivity, and whether these changes can be detected shortly after infusion or seven days later.

Hypothesis 1: Ketamine group would show acute increases in motivated decision making (i.e., greater acceptance of higher effort-higher reward offers) compared with placebo, and that these changes would remain at Day 7.

Aim 2: To investigate whether ketamine produces specific changes in the reward and effort sensitivity.

Hypothesis 2: Ketamine would increase reward sensitivity (steeper reward slopes) and reduce sensitivity to effort costs, leading to greater acceptance of high reward/high effort combinations compared with placebo.

Methods

Study Design

A detailed description of recruitment, screening, and infusion procedures is provided in Chapter 3. Briefly, participants were adults with treatment-resistant depression (TRD) enrolled in a randomised, double-blind, placebo-controlled experimental medicine study. Participants were randomised to receive a single intravenous infusion of ketamine (0.5 mg/kg) or saline placebo

(0.9%) under double-blind conditions. A schematic overview of the study design is shown in **Figure 6.1.**

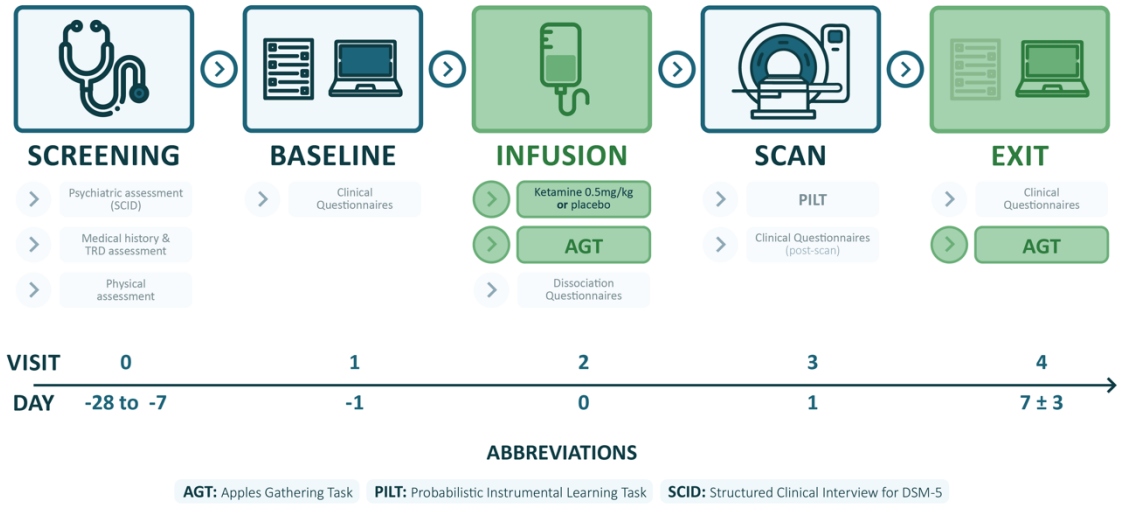


Figure 6.1. Study design and timeline. Following screening and baseline assessment, participants received a randomised infusion of ketamine or placebo (Day 0). The Apples Gathering Task (AGT) was administered 30 minutes post-infusion (Day 0) and 7 days post-infusion (Day 7) (highlighted in green).

Participants

Of the 60 participants enrolled, 59 were included in the 30-minute post-infusion analysis (T1; ketamine = 28, placebo = 31). Data were not collected at T1 for one participant due to a task error at the infusion visit. At the 7 days post-infusion (T2), 57 participants were included (ketamine = 27, placebo = 30). One participant did not attend the follow-up visit and provided no T2 data. A second participant was unable to attend in person due to personal circumstances and did not complete the T2 task.

Procedure

The Apples Gathering Task (AGT) was administered at two post-infusion time points: 30 minutes following infusion (T1; rapid effects) and 7 days following infusion (T2; sustained effects). At each time point, participants completed the AGT.

Apple Gathering Task (AGT)

The Apples Gathering Task (AGT) is a physical effort-based decision-making task designed to assess motivation to exert effort for reward (Bonnelle et al., 2015). The task was designed in Psychtoolbox (psychtoolbox.org) using MATLAB and administered on a laptop computer. Physical effort was measured using a handheld dynamometer (SS25LB, BIOPAC Systems) which participants squeezed with their non-dominant hand to obtain rewards.

Maximum Voluntary Contraction Calibration

Prior to the task, participants completed six trials to estimate their maximum voluntary contraction (MVC). Effort levels during the task were calibrated relative to each participant's MVC to ensure task demands were individualised to physical capacity.

Task Structure

The AGT consisted of two phases: an offer phase and a work phase.

Offer Phase

On each trial of the offer phase, participants were presented with an offer indicating how much physical effort they had to exert for a set amount of reward. Effort levels were defined as five levels (16, 32, 48, 64, 80% MVC) and reward levels were defined as five point values (1, 4, 7, 10, 13 points).

Offers were visually presented in the form of an apple tree, where the number of apples indicated the reward available in the trial and the effort levels were represented by horizontal lines on the tree trunk. A red line indicated the effort required on that trial, with higher positions corresponding to greater force requirements, five being the max (80% MVC).

Participants were free to accept or reject offers based on their own perception of the effort–reward combination. Participants were informed that the goal of the task was to think about each offer carefully and think is the offer worth it. Responses were made using the keyboard, with "yes" and "no" responses mapped to the left and right arrow keys, and response mapping counterbalanced across trials to ensure attention. The task was self-paced, and participants were free to accept or reject as many offers as they wished. Rejected offers and failed trials resulted in zero points. No physical effort was required during the offer phase.

Work Phase

To minimise fatigue effects, the work phase consisted of a subset of ten offers randomly selected from the offer phase. If an offer was presented, participants were required to squeeze the dynamometer above the specified force level and maintain this force continuously for at least four seconds to obtain the reward (collect the apples). Visual feedback was provided to indicate applied force. If a previously rejected offer was presented, participants were instructed not to squeeze the dynamometer and no reward was obtained.

Across the task, five reward levels and five effort levels were orthogonally combined to produce 25 unique reward-effort conditions. These conditions were presented in a pseudo-randomised order across five blocks, resulting in a total of 125 trials. The task lasted approximately 25 minutes.

Schematic representations of the offer and work phases are shown in **Figures 6.2 and 6.3**.

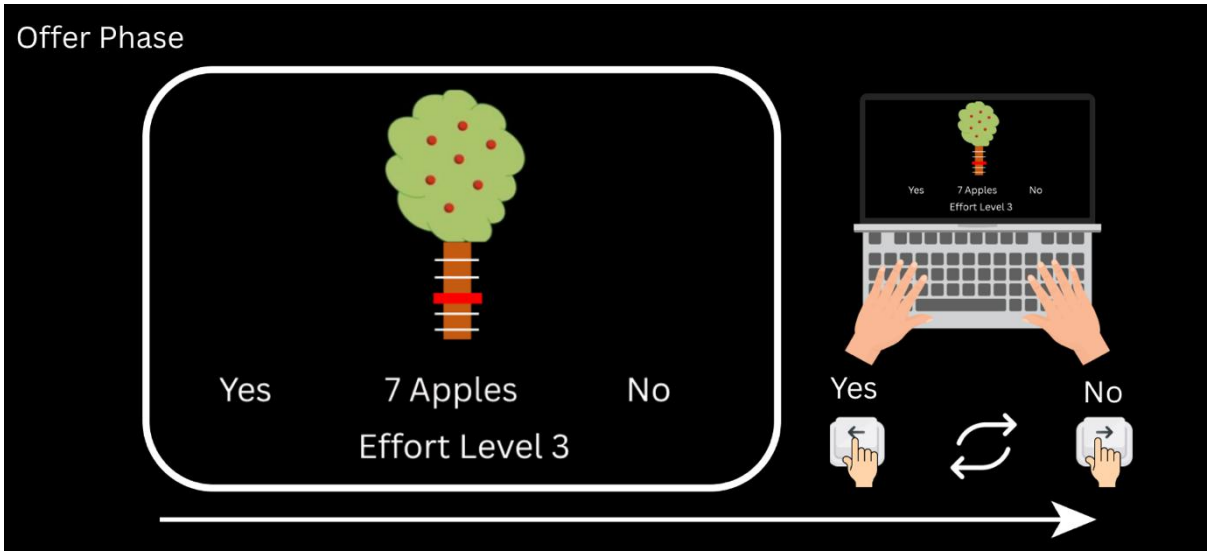
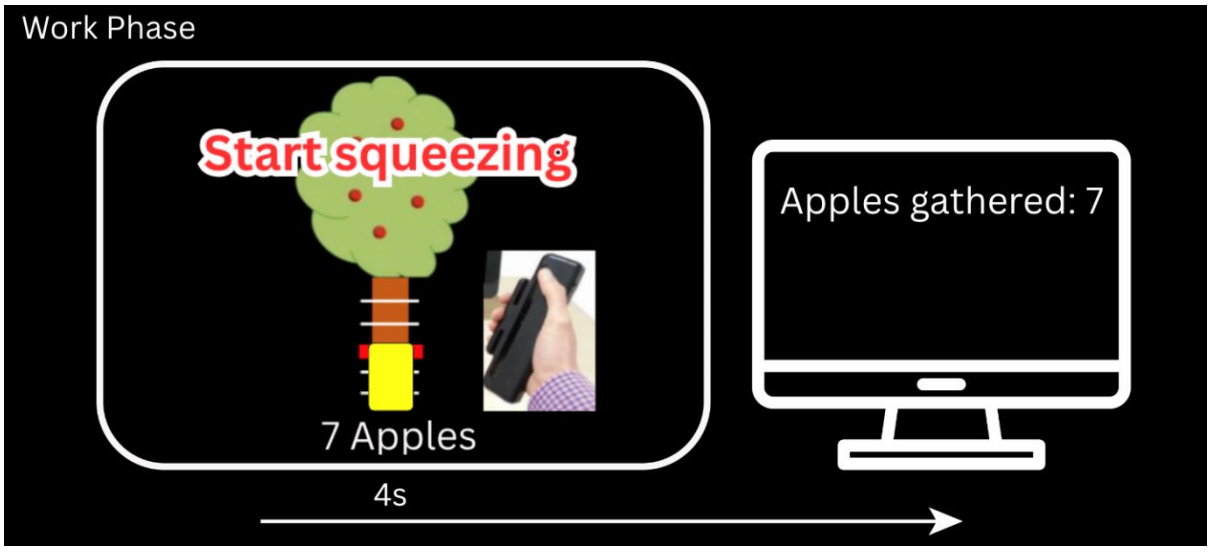


Figure 6.2 Example trial of the offer phase of the AGT. The task was split into two phases: offers Phase and Work Phase. During decision phase, each trial participants were presented with a reward-effort combination offer. Participants decided if they wanted to accept or reject the offer based on the number of points (apples) and effort level (grip force). Participants were free to accept and reject as many offers as possible. The participant responded using the arrows on the keyboard with the yes and no changing sides throughout the task which the participant was aware.



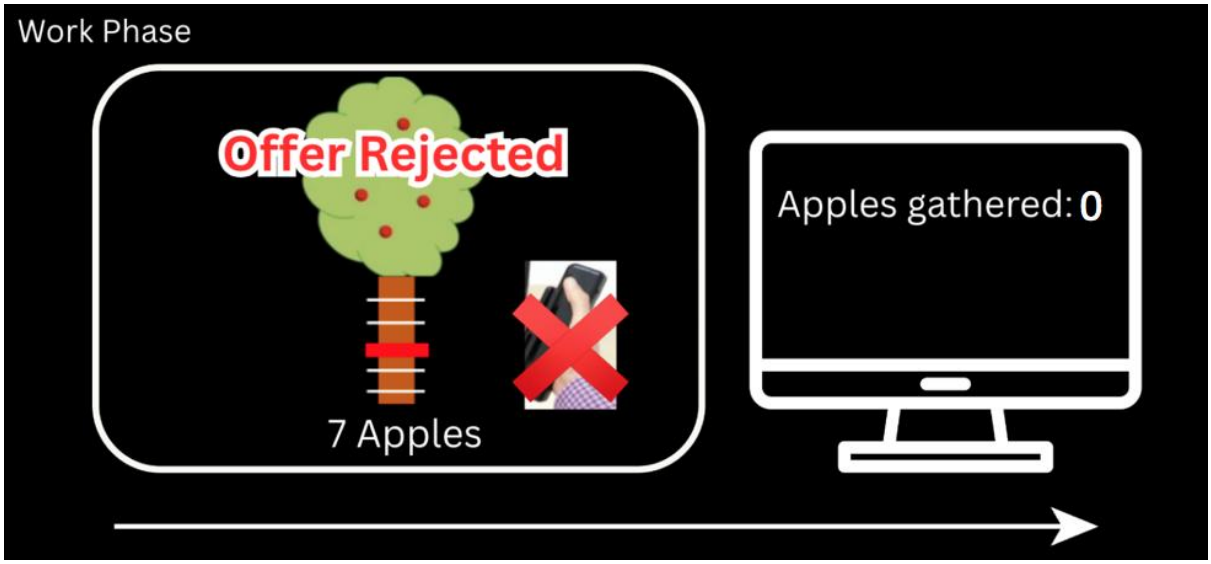


Figure 6.3. Example trial of the work phase of the AGT. Work Phase consisted of 10 random offers that could be a mix of either accepted or rejected. If a 'yes' offer appeared, the participant would be required to start squeezing the dynamometer just above the red line for 3 consecutive seconds, when squeezing, a yellow bar would appear to show the participant's force. After squeezing, feedback would appear on the screen. If a 'no' offer appeared, the participant was instructed to sit and not use the dynamometer, and no points would be won. There are five different reward levels (1,4,7,10,13 points) and five different effort levels 16, 32, 48, 64, 80% MVC.

Behavioural data processing

AGT data were pre-processed using custom MATLAB scripts. Raw task outputs were provided as. mat files, each containing a result structure with trial-level task data and practice trials. These were converted into MATLAB tables and combined into single trial-level dataset. An unmodified version of the merged dataset was kept as a raw reference file.

Participants with an overall offer acceptance rate below 10% were excluded from further analyses as it indicates poor engagement in the task and therefore does not provide a reliable estimate of effort-reward decision-making.

Reaction times (RTs) from the offer phase were expressed in milliseconds. Extreme RT values were removed at the trial level using a +- 3 SD rule, calculated separately for each participant and time point. Cleaned trial-level datasets and participant-level summaries were then generated for the analysis.

The trial-level dataset included subject ID, group, time point, reward level, effort level, choice (accept/reject), and reaction time. For the offer phase, per-participant acceptance rates and trial counts were calculated. The dataset was then separated into the offer stage and the work phase to reflect the task structure.

Statistical Analysis

Apples Gathering Task

Offer acceptance

Offer acceptance was analysed using generalised linear mixed-effects models (GLMMs) with a logistic link function to investigate the effects of reward, effort, group and time point on choice behaviour. Analyses were performed in R (version 4.4.3) using the lme4 package.

Statistical model specification

A combined model was specified as the primary model, including reward level, effort level, group (ketamine vs placebo), and time point (T1 vs T2) as fixed effects, along with all interactions. This model allowed direct testing of whether reward and effort sensitivity differed between groups and whether these effects changed across time. A random intercept for subject was included to account for repeated trials within participants:

$$\text{Accept} \sim \text{reward} * \text{effort} * \text{group} * \text{timepoint} + (1 \mid \text{subject})$$

Reward and effort were treated as continuous numeric predictors (levels 1–5) to estimate linear changes in acceptance probability across increasing reward and effort levels.

To examine effects at individual time points, additional models were fitted separately for each time point, including reward, effort, and group as fixed effects and a random intercept for subject:

$$\text{Accept} \sim \text{reward} * \text{effort} * \text{group} + (1 \mid \text{subject})$$

These time point-specific models were conducted as follow-up analyses to examine the pattern of effects identified in the combined model.

Where models including random slopes failed to converge, simplified models including random intercepts only were used.

Where significant or trend-level interactions were observed, follow-up analyses were conducted to explore simple effects. Condition-level simple slopes were estimated using the emtrends function from the emmeans package in R. This provided estimates of reward and effort slopes (i.e., the effect of reward or effort on acceptance probability) for each combination of group (ketamine vs placebo) and time point (T1 vs T2). Pairwise comparisons of these slopes were used to determine whether reward or effort sensitivity differed between groups or changed over time.

Reaction Times (RT)

Reaction times from the offer phase were log-transformed to reduce positive skew and analysed using linear mixed-effects regression models (LMERs). The analysis was performed in R using the lme4 package.

Statistical model specification

A combined model was specified as the primary model, including reward level, effort level, group (ketamine vs placebo), and time point (T1 vs T2) as fixed effects, along with all interaction terms. This model allowed direct testing of whether the effects of reward and effort on reaction time differed between groups and whether these effects changed across time. A random intercept for subject was included to account for repeated observations within participants:

$$logRT \sim reward_num * effort_num * group * timepoint + (1 | subject)$$

Reward and effort were treated as continuous numeric predictors (levels 1–5) to estimate linear changes in reaction time across increasing reward and effort levels.

To examine effects within each timepoint, additional models were fitted separately for each timepoint, including reward, effort, and group as fixed effects and a random intercept for subject:

$$logRT \sim reward_num * effort_num * group + (1 \mid subject)$$

These timepoint-specific models were conducted as follow-up analyses to examine the pattern of effects identified in the combined model.

Where models including random slopes failed to converge, simplified models including random intercepts only were used.

Where significant or trend-level interactions were observed, follow-up analyses were conducted to examine simple effects. Condition-level simple slopes were estimated using the *emtrends* function from the emmeans package in R. Pairwise comparisons of these slopes were used to determine whether the effects of reward or effort on reaction time differed between groups or changed across time.

Results

Participants

The final analysis included 58 participants at 30 minutes post-infusion (28 ketamine; 30 placebo) and 56 at 7 days post-infusion (27 ketamine and 29 placebo). One participant was excluded due to an overall offer acceptance rate below 10%, and one participant was unable to attend the 7 days post-infusion visit. **Table 6.1** presents demographic and clinical characteristics of the final sample.

	Ketamine (N=28)	**Placebo (N=30)**
Sociodemographic variables		
Age years — mean ± SD	29.71 (10.88)	32.20 (10.66)
Female, n (%)	18 (64.29%)	20 (66.67%)
Years of education — mean ± SD	16.86 (2.21)	17.57 (3.39)
Ethnicity, n (%)		
White	24	22
Mixed/Multiple ethnic groups	2	1
Asian/Asian British	1	4

Black/African/Caribbean/Black British	1	-
Other ethnic group	-	1

Clinical variables	Ketamine (N = 28)		Placebo (N = 30)	
	Pre-infusion	Post-infusion (7 days)	Pre-infusion	Post-infusion (7 days)
HAM-D	16.54 (4.32)	10.22 (4.43)	17.58 (2.95)	12.97 (5.26)
QIDS	17.93 (3.71)	9.85 (4.56)	17.73 (5.14)	12.14 (5.87)
TEPS Total	65.46 (12.52)	67.11 (16.48)	69.13 (12.36)	71.41 (10.91)
Anticipatory	34.43 (6.51)	34.11 (9.33)	35.87 (8.43)	36.14 (7.77)
Consummatory	31.04 (6.69)	33.00 (8.10)	33.27 (6.03)	35.28 (5.70)
AMI	3.12 (0.20)	3.09 (0.22)	3.16 (0.22)	3.07 (0.18)
Behavioural activation	2.97 (0.27)	2.97 (0.40)	3.03 (0.31)	2.97 (0.31)
Emotional sensitivity	3.54 (0.43)	3.34 (0.49)	3.63 (0.47)	3.41 (0.44)
Social motivation	2.85 (0.32)	2.96 (0.33)	2.81 (0.38)	2.84 (0.32)

Table 6.1. Demographic and questionnaire scores of the ketamine and placebo groups pre-infusion and post-infusion. This table includes final AGT sample size only; full sample is reported in Chapter 3 (Methods). Post-infusion scores are missing for two participants who were unable to attend 7 days post-infusion. *data on ethnicity and years of education are missing for two participants (both placebo). Categories are based on the UK Office for National Statistics

(ONS) 2021 classification. The "White" category includes participants identifying as English, Welsh, Scottish, Northern Irish or British, and those reporting any other White background (e.g., Polish, Russian, Portuguese, South African, European). The "Mixed/Multiple ethnic groups" category includes participants identifying with more than one ethnic background (e.g., White and Black African, White and Asian, or other mixed combinations).

Offer Acceptance

Combined model across time points

Offer acceptance was analysed using a mixed-effects logistic regression including reward, effort, group, and time point, and all interactions.

There were significant main effects of both reward [$\beta = 1.32$, SE = 0.12, $z = 10.65$, $p < 0.001$] and effort [$\beta = -1.14$, SE = 0.10, $z = -11.23$, $p = <0.001$], such that an increasing reward predicted increased probability of accepting offers, whereas increasing effort predicted a reduced probability of accepting offers. These main effects were qualified by a significant reward x effort interaction [$\beta = 0.14$, SE = 0.04, $z = 3.79$, $p < 0.001$].

Reward sensitivity differed across time points, as reflected by a significant reward x time point interaction [$\beta = 0.39$, SE = 0.19, $z = 2.10$, $p = 0.04$], indicating that the effect of reward magnitude on acceptance probability differed between T1 and T2. Effort sensitivity also differed across timepoints, as indicated by a significant effort x time point interaction [$\beta = 0.36$, SE = 0.14, $z = 2.59$, $p = 0.01$].

There was no significant main effect of group [$\beta = 0.09$, SE = 0.60, $z = 0.15$, $p = 0.88$], indicating no overall difference in acceptance probability between the ketamine and placebo groups across

time points. There was also no evidence of a group difference in reward sensitivity, as reflected by a non-significant reward x group interaction [β = -0.15, SE = 0.17, z = -0.86, p =0.38)]

However, there was trend-level evidence for a reward by group x time point interaction [β = -0.45, SE = 0.24, z = -1.87, p = 0.06] suggesting that changes in reward sensitivity over time may have differed between groups (**Figure 6.4**).

T1 (30 minutes post-infusion)

To clarify these effects, follow-up models were performed separately at each time point.

At T1, there were significant main effect of reward [β =1.44, SE = 0.13, z = 10.74, p <0.001] and effort [β = -1.29, SE =0.11, z = -11.36, p <0.001], such that an increasing reward increased acceptance of offers, whereas increasing effort reduced acceptance of offers. These effects were qualified by a significant reward x effort interaction [β = 0.16, SE=0.04, z=4.11, p <0.001], indicating that reward had a greater effect on acceptance at higher effort levels.

There was trend-level evidence for a reward x group interaction [β = -0.32, SE = 0.18, z = -1.78, p = 0.07], indicating reduced sensitivity in the ketamine group relative to the placebo group. Specifically, the ketamine group showed a trend towards accepting fewer high-reward offers than placebo (**Figure 6.4**).

There was no effort x group interaction (p > .05), indicating that ketamine and placebo participants did not differ in effort sensitivity. There was also no reward x effort x group interaction (p > .05), indicating that the reward by effort interaction did not differ between groups.

T2 (one week post-infusion)

At T2, there were significant main effects of reward [β = 1.74, SE = 0.16, z = 10.61, p = <0.001] and effort [β = -1.29, SE=0.13, z = -9.73, p <0.001], such that increasing reward increased acceptance of offers, whereas increasing effort reduced acceptance of offers. A significant reward x effort interaction was also observed [β = 0.14, SE = 0.05, z = 3.13, p = 0.002], indicating that reward had a greater effect on acceptance at higher effort levels.

Importantly, there was a significant reward x group interaction [β = -0.51, SE=0.20, z=-2.52, p = 0.01], indicating a group difference in reward sensitivity. Specifically, the ketamine group accepted fewer moderate to high reward level offers than the placebo group (**Figure 6.4**).

There was no effort x group interaction (p > .05), indicating that ketamine and placebo participants did not differ in effort sensitivity. There was also no reward x effort x group interaction (p > .05), indicating that the reward by effort interaction did not differ between groups.

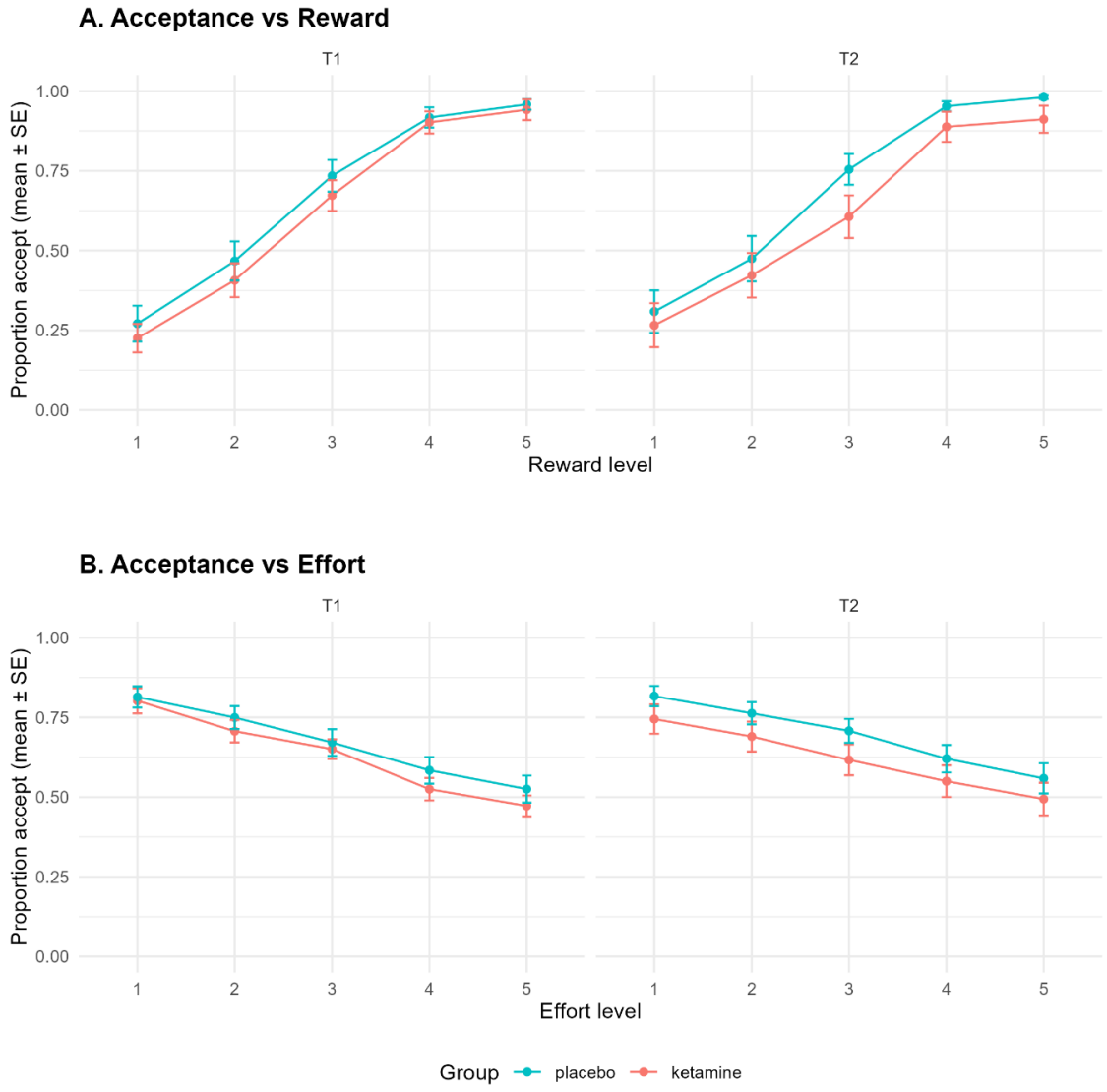


Figure 6.4. Acceptance probability by reward level (A) and effort level (B) at T1 and T2. Acceptance probability is shown separately for the placebo and ketamine groups at 30 minutes post-infusion (T1) and one week post-infusion (T2). Panel A shows acceptance probability across reward magnitude levels, collapsed across effort levels. Panel B shows acceptance probability across effort levels, collapsed across reward magnitude levels. Points represent group means calculated from subject-level acceptance probabilities, and error bars indicate ±1 standard error of the mean across participants. Across groups and timepoints, acceptance probability increased with reward magnitude and decreased with effort level, consistent with sensitivity to reward and effort

costs. At T2, ketamine participants showed reduced reward sensitivity compared with placebo participants, reflected in smaller increases in acceptance as reward magnitude increased and fewer accepted high-reward offers.

Summary

Choice behaviour was strongly influenced by both reward magnitude and effort level. Increasing reward increased acceptance of offers, whereas increasing effort reduced acceptance of offers.

Reward sensitivity and effort sensitivity varied across time points. Follow-up analyses indicated a group difference in reward sensitivity at T2. Specifically, the ketamine group showed reduced reward sensitivity, reflected in fewer accepted high-reward offers compared with placebo.

Reaction Time (RT)

A total of 289 offer trials were excluded based on the RT ±3 SD outlier rule.

Combined model (across time points)

Reaction times were analysed using linear mixed-effects regression including reward, effort, group, and time point, and all interactions.

There was a significant main effect of reward [β = -0.04, SE =0.01, t(13,890)=-4.16, p = <0.001], such that increasing reward reduced reaction times. There was no significant main effect of effort level [β = -0.01, SE = 0.01, t(13,890) = -1.43, p = 0.1], indicating that effort level did not significantly affect reaction times.

There was a significant reward x effort level interaction [β = 0.009, SE = 0.003, t(13,890) = 2.94, p = 0.003], indicating that the effect of reward on reaction time differed across effort levels.

There was also a significant reward x group interaction [β =-0.03, SE=0.01, t(13,890) = -2.27, p = 0.02], indicating a group difference in reward sensitivity. Specifically, ketamine group showed greater reward sensitivity than placebo, reflected in a larger reduction in reaction time as reward increased (**Figure 6.5**).

There was a trend-level reward by group by time point interaction [β =0.04, SE=0.02, t(13,890) = 1.74, p = 0.08], indicating that group differences in reward sensitivity varied across time points (**Figure 6.5**).

T1 (30 minutes post-infusion)

At T1, there was a significant main effect of reward [β = -0.04, SE = 0.01, t(7,046) = -4.21, p <0.001], such that increasing reward reduced reaction times. There was also a significant reward x effort interaction [β =0.01, SE = 0.003, t(7,046) = 2.97, p = 0.003], indicating that the effect of reward on reaction time differed across effort levels.

Importantly, there was a significant reward x group interaction (β = -0.03, SE=0.01, t(7,046)= -2.32, p = 0.02), indicating a group difference in reward sensitivity. Both groups showed faster reaction times as reward increased however, the ketamine group showed greater reward sensitivity than placebo participants, reflected in a larger reduction in reaction time as reward increased (**Figure 6.5**). Although, overall reaction times were slower in the ketamine group. There was no main effect of group (p > .05), indicating no overall difference in reaction times between groups.

T2 (one week post-infusion)

At T2, there was a significant main effect of reward [(β = -0.05, SE = 0.009, t(6792) = -5.58, p <0.001)], such that increasing reward reduced reaction times. There was also a significant reward

by effort interaction [(β = 0.08, SE = 0.003, $t(6792) = 3.18$, $p < 0.001$)], indicating that the effect of reward on reaction time differed across effort levels.

There was no significant reward x group interaction ($p > .05$), indicating no group difference in reward sensitivity at T2 (**Figure 6.5**). There was also no main effect of group ($p>0.05$) indicating no overall difference in reaction times between ketamine and placebo.

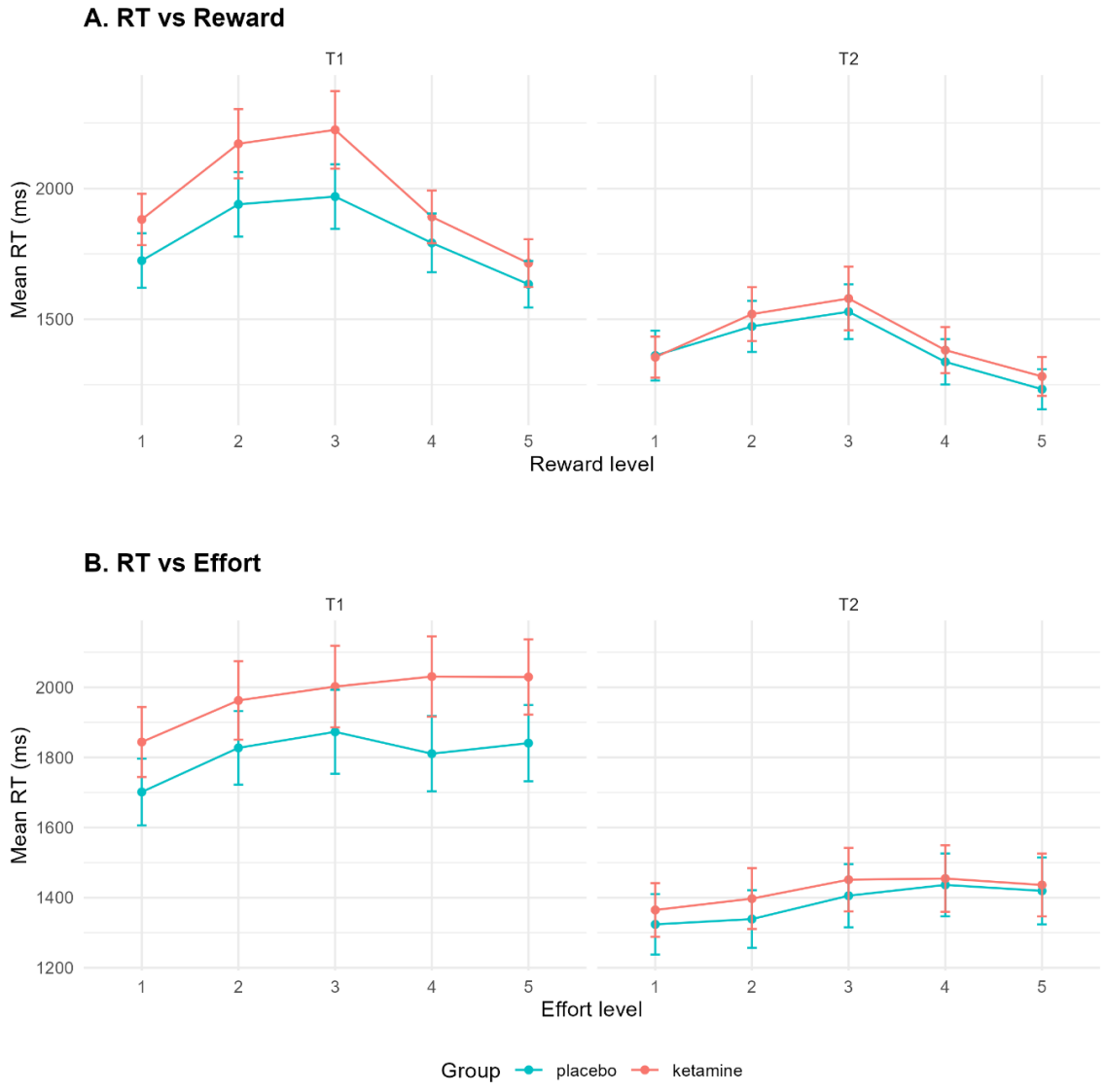


Figure 6.5. Reaction time by reward level and effort level at T1 and T2. Mean reaction time (RT; ms) is shown by reward level (A) and effort level (B) for the placebo (blue) and ketamine (red/orange) groups at 30 minutes post-infusion (T1) and one week post-infusion (T2). Points

represent group means derived from subject-level averages; error bars indicate ±1 standard error of the mean. At T1, ketamine participants showed greater reward-related speeding of responses than placebo participants, reflected in a larger reduction in reaction time as reward magnitude increased. This is consistent with a significant reward x group interaction at T1. At T2, there was no reward x group interaction, indicating that ketamine and placebo participants did not differ in reward-related modulation of reaction time at follow-up. Reaction time increased with effort level similarly across groups, indicating comparable effort-related effects on response speed.

Summary

There was greater reward-related speeding of responses in the ketamine group at T1, reflected in a larger reduction in reaction time as reward increased compared with placebo. There was no reward x group interaction at T2, indicating that ketamine and placebo participants did not differ in reward-related modulation of reaction time at follow-up.

Discussion

This chapter examined performance on the Apple Gathering Task (AGT) at two time points to investigate the acute and delayed effects of a single ketamine infusion on effort-based decision-making. Depression is characterised by impairments in reward processing and motivation, including reduced reward sensitivity and altered effort expenditure (Treadway & Zald, 2011). The AGT was used because it allows the independent contributions of reward magnitude and effort cost to acceptance behaviour to be examined (Bonnelle et al., 2015). This study therefore tested whether ketamine altered reward sensitivity and effort sensitivity during value-based choice, and reward-related modulation of reaction time, shortly after infusion (T1; 30 minutes) and at follow-up (T2; one week).

Contrary to the original hypotheses, ketamine did not increase acceptance of high-reward offers or increase reward sensitivity overall. Instead, the ketamine group showed differences in the effect of reward magnitude on behaviour in a time-dependent manner. Shortly after infusion (T1), the ketamine group showed significant differences in the effect of reward magnitude on reaction time, whereas one week later (T2), ketamine group showed differences in the effect of reward magnitude on acceptance behaviour. These findings indicate that ketamine did not produce a general increase in motivation, but instead showed differences in how reward magnitude influenced behaviour. This pattern suggests that ketamine affected components of reward-guided decision-making, rather than producing a uniform increase in willingness to exert effort.

Across participants, acceptance behaviour showed the expected pattern. Increasing reward increased acceptance of offers, whereas increasing effort reduced acceptance of offers. Reward and effort also interacted, such that reward had a greater effect on acceptance at higher effort levels. Importantly, overall acceptance rates did not differ between ketamine and placebo groups. This indicates that ketamine did not increase overall willingness to accept offers or exert effort. Instead, group differences were specific to the effect of reward magnitude on acceptance behaviour. This finding indicates a difference in reward sensitivity rather than a general difference in task engagement or effort tolerance, consistent with models in which reward sensitivity and effort sensitivity represent separable influences on acceptance decisions (Pessiglione et al., 2018; Shadmehr et al., 2016).

There was trend-level evidence for a reward x group x time point interaction in the combined model, which was explored using time point specific analyses. At T1, reward and effort influenced acceptance behaviour in the expected directions, and there was no significant reward x group interaction. This indicates that the effect of reward magnitude did not differ between groups shortly after infusion. Although preclinical work suggests that ketamine can rapidly modulate

glutamate and dopamine transmission within minutes (Kokkinou et al., 2018; Moghaddam et al., 1997), the timing of any behavioural changes in humans is uncertain. The study did not observe significant changes in effort-reward decision making 30 minutes after infusion. This may reflect limits in translating very early rodent neurochemical effects to human behaviour, or it may be that these early effects require more time before they translate into observable behaviour.

In contrast, at follow-up (T2), there was a significant reward x group interaction. Ketamine participants showed reduced reward sensitivity compared with placebo participants, reflected in smaller increases in acceptance as reward increased. Specifically, ketamine participants accepted fewer high-reward offers than placebo participants. Importantly, overall acceptance rates and effort sensitivity did not differ between groups. This indicates that ketamine showed altered reward sensitivity without affecting overall willingness to exert effort. Because both groups consisted of individuals with treatment-resistant depression and no pre-infusion baseline, this difference cannot be interpreted as improvement or impairment relative to baseline. Instead, these findings indicate that ketamine showed differences in the effect of reward magnitude on acceptance behaviour one week post-infusion. This interpretation is consistent with evidence that ketamine influences reward-related behaviour (Krystal et al., 2019; Lally et al., 2014).

Reaction time findings showed a different temporal pattern. Across participants, increasing reward reduced reaction times, consistent with established effects of reward magnitude on response speed. At T1, there was a significant reward x group interaction, indicating that reward had a greater effect on reaction time in the ketamine group compared with the placebo group. Specifically, participants in the ketamine group showed larger decrease in reaction time as reward level increased relative to those in the placebo group. This indicates that the ketamine group showed differences in the effect of reward magnitude on response speed shortly after infusion.

There was no reward x group interaction at T2, indicating that ketamine and placebo participants did not differ in reward-related modulation of reaction time at follow-up. These findings suggest that ketamine produced a transient change in reward-related modulation of reaction time shortly after infusion.

These findings indicate that ketamine participants showed differences in distinct components of reward-guided behaviour at different time points. Shortly after infusion, the ketamine group showed differences in reward-related modulation of response speed. One week later, the ketamine group showed differences in reward sensitivity during acceptance decisions. This distinction indicates that reward-related modulation of reaction time and reward sensitivity during acceptance behaviour represent separable behavioural processes that can show different temporal patterns in ketamine and placebo groups.

Reduced reward sensitivity at follow-up was reflected in a flatter relationship between reward magnitude and acceptance behaviour in the ketamine group. This indicates that reward magnitude had less influence on acceptance behaviour in ketamine participants compared with placebo participants. Importantly, ketamine did not increase overall acceptance rates or effort sensitivity, indicating that ketamine did not produce a general increase in motivation. Instead, ketamine altered how reward magnitude influenced value-based decision-making. This interpretation is consistent with computational accounts in which reward magnitude and effort cost represent separable influences on acceptance behaviour (Husain & Roiser, 2018; Pessiglione et al., 2018).

In summary, ketamine did not increase overall willingness to accept offers or exert effort. Instead, ketamine showed differences in reward sensitivity in a time-dependent manner. Shortly after infusion, ketamine showed greater reward-related speeding of responses, whereas at follow-up ketamine showed reduced sensitivity during acceptance decisions, reflected in fewer accepted high-

reward offers compared with placebo. These findings indicate that the ketamine group showed differences in how reward magnitude influenced behaviour, rather than producing a general increase in motivation. This interpretation is consistent with evidence that ketamine modulates neural systems involved in reward and value processing, including frontostriatal circuits involved in valuation and action selection (Husain & Roiser, 2018; Krystal et al., 2019; Lally et al., 2014).

Strengths and limitations

Several strengths of this study warrant consideration. The AGT allows reward and effort parameters to be examined independently, addressing limitations of other effort-based decision-making tasks. The two-timepoint design enabled investigation of both acute and delayed effects, providing insight into the temporal dynamics of ketamine's behavioural effects. However, several limitations should also be considered. The absence of a pre-infusion baseline limits conclusions about within-participant changes over time. Also, behaviour was not assessed during the intermediate period between T1 and T2, which may be informative given evidence that ketamine's behavioural and clinical effects evolve over several days. In addition, the AGT focuses on physical effort and may not capture other relevant domains of motivation, including cognitive or social effort.

Future research could assess effort-based decision-making at additional time points, particularly within the 24-72-hour window during which ketamine's clinical effects are thought to peak. Computational modelling approaches, including drift diffusion modelling, may help clarify whether ketamine alters reward valuation, decision policy, or value-to-action translation by jointly modelling choices and reaction times. Examining associations between reward sensitivity and behavioural or clinical measures of motivation, including social motivation and apathy, may also

provide further insight into the mechanisms linking reward processing and motivational symptoms.

In summary, ketamine did not increase overall willingness to accept offers or exert effort on the AGT. Instead, ketamine participants showed time-dependent differences in how reward magnitude shaped behaviour: shortly after infusion, reward exerted a stronger influence on response, whereas at follow-up reward exerted a weaker influence on acceptance decisions, consistent with reduced reward sensitivity. Together, these findings indicate that ketamine did not produce a general enhancement of motivation, but altered the contribution of reward information to value-guided behaviour. One interpretation is that ketamine shifted how reward magnitude was weighted or integrated during valuation, changing the extent to which reward guided choice without altering effort sensitivity or overall task engagement. This account is consistent with evidence that ketamine influences neural systems supporting reward and value processing and with the present thesis findings of ketamine-related modulation of neural responses to outcomes and prediction-error signalling (Chapter 5). More broadly, the distinction between early effects on response speed and later effects on valuation suggests that behavioural consequences may unfold over different timescales than acute pharmacological effects, highlighting the importance of assessing both immediate and delayed components of motivated behaviour.

Chapter 7: General Discussion

Reward processing as a mechanistic bridge between symptoms and treatment

As outlined in the General Introduction, Major Depressive Disorder (MDD) is a leading cause of disability worldwide and is highly heterogeneous in symptom presentation, illness course, and treatment response. This heterogeneity poses a challenge for both clinical practice and research, particularly when depression is conceptualised primarily through symptom-based measures. Although symptom measures are important in clinical settings, they provide limited insight into the neurocognitive mechanisms that give rise to persistent impairment and individual differences in treatment outcome. These limitations have motivated a shift in mechanistic approaches that focus on specific neurocognitive processes that may be more directly engaged by treatment.

Reward processing provides a useful framework for investigating such mechanisms in depression. Reward-guided behaviour supports everyday functioning by enabling individuals to learn from outcomes, assign value to actions, and decide whether to pursue or avoid future opportunities. Importantly, reward processing consists of multiple distinct components, including anticipation, valuation, effort expenditure, outcome evaluation, and learning from feedback (Husain & Roiser, 2018). Disruption at different stages of this process may give rise to similar clinical presentations through distinct underlying mechanisms.

The central aim of this thesis was to explore reward and loss processing in depression across behavioural, computational, neural, and clinical levels, and to determine how these components are modulated by antidepressant treatments. Across two studies and four data chapters, hypotheses were tested in individuals with depression and treatment-resistant depression using a range of reinforcement learning and effort-based decision-making paradigms alongside symptom measures and neuroimaging.

Overview of main findings

Across studies, alterations were most consistently observed in learning from negative feedback, rather than reward sensitivity. In Study 1, greater depressive symptom severity was associated with reduced updating following negative (loss) outcomes, reflected in lower loss learning rates, with no association with loss-optimal choice accuracy. In contrast, within the clinically diagnosed MDD subgroup, conventional antidepressant use was associated with a different profile, characterised by higher loss learning rates, reduced decision stability (lower inverse temperature) and poorer loss-optimal choice accuracy, independent of symptom severity. Overall, these findings indicate that depressive symptom severity and antidepressant use relate to distinct patterns of loss-related learning and value-guided behaviour.

Study 2 extended these findings by examining reward and loss processing in treatment-resistant depression using behavioural, computational, neural, and clinical measures. At 24 hours post-infusion, ketamine selectively modulated neural responses during outcome processing, increasing differentiation between reward and loss outcomes and enhancing responses to loss avoidance (no-loss) across cortico-striato-limbic circuitry. These neural effects occurred in the absence of concurrent changes in behavioural task performance or in estimated learning parameters, including learning rates and inverse temperature.

Ketamine did not produce clear acute behavioural effects on motivation or effort expenditure. However, a selective reaction time difference for high-effort offers was observed 30 minutes post-infusion, and a group difference in reward sensitivity emerged at 7 days post-infusion. Clinically, depressive symptoms improved over time, although early ketamine-specific clinical effects were difficult to detect, likely due to a substantial placebo response. Assessing symptom changes provided important clinical context for interpreting the neurocognitive findings and situating them within the broader effects of ketamine.

Overall, these findings highlight the importance of considering loss-related processes alongside reward sensitivity when investigating depression and antidepressant treatments.

Depression and loss processing in instrumental learning

Reinforcement learning impairments have been consistently implicated in depression, particularly in relation to how individuals learn from reward and aversive outcomes (Admon & Pizzagalli, 2015; Eshel & Roiser, 2010; Huys et al., 2013). However, findings remain heterogeneous across tasks and samples, with evidence for both heightened and blunted aversive learning depending on task structure and clinical profiles. Within this thesis, effects were valence-specific and most consistently observed in the aversive condition (loss) during instrumental learning.

In Study 1, greater depressive symptom severity was associated with reduced learning rates during loss trials, with no association observed for reward learning or choice stochasticity. Although this appears to contrast with simulation meta-analysis findings (Pike & Robinson, 2022) reporting increased punishment learning rates in depression, loss learning in a probabilistic instrumental learning task reflects avoidance and safety learning under uncertainty rather than passive loss/aversive sensitivity. Within a predictive-processing framework, learning rates can be interpreted as indexing the relative weighting of prediction errors against prior beliefs during belief updating. In the PILT, outcomes are probabilistic but relatively stable, such that effective performance requires integrating feedback over time rather than rapid trial-by-trial updating. Reduced loss learning rates in this context may therefore reflect rigid negative expectations and reduced flexibility in updating avoidance policies, consistent with over-weighted priors and under-weighted prediction errors (Gilbert et al., 2022; Kube et al., 2020). From this perspective, depression may be characterised not by heightened reactivity to aversive outcomes, but by

constrained belief updating that limit learning from both negative outcomes and signals of safety or relief (no loss).

Conventional antidepressants and loss processing in instrumental learning

A distinct pattern emerged when examining associations between antidepressant use and reinforcement learning within the clinically diagnosed MDD subgroup. Antidepressant use was associated with higher loss learning rates, lower loss inverse temperature, and reduced loss optimal choice accuracy, even after controlling for symptom severity and demographic factors. Crucially, this pattern was directionally opposite to the association observed with depressive symptom severity, indicating that antidepressants and depression severity have different and potentially opposing alterations on aversive learning.

Higher loss learning rates indicate stronger trial-by-trial updating following negative outcomes, whereas a lower inverse temperature reflects reduced control of choice behaviour by learned values. Within a stable probabilistic environment, this combination may bias behaviour toward heightened sensitivity to negative outcomes, rather than the gradual integration of feedback across trials. These findings are consistent with cognitive neuropsychological models proposing that antidepressants modulate affective and cognitive processing prior to observable mood change (Harmer et al., 2009, 2017). Within this framework, higher loss learning rates may reflect reduced rigidity in updating negative expectations, while lower inverse temperature may reflect reduced consistency in how learned values guide behaviour under conditions of aversive uncertainty.

Ketamine and loss processing in instrumental learning

At 24 hours post-infusion, ketamine was associated with increased neural differentiation between win and loss outcomes during outcome processing across cortico-striato-limbic regions implicated

in valuation and salience processing, including the striatum, insula, thalamus, medial temporal regions, and prefrontal cortex. This pattern reflected attenuated responses to loss outcomes alongside enhanced responses to reward and loss-avoidance (no-loss) outcomes compared with placebo. Although responses to win outcomes were significantly greater in the ketamine group, these effects occurred in the absence of changes in reward learning, anticipation, or behavioural performance. The findings are therefore more consistent with a reweighting of outcome information, characterised by reduced impact of aversive outcomes and increased sensitivity to better-than-expected signals of safety, rather than a general increase in reward responsiveness.

In contrast, the placebo group showed greater loss-related activation relative to no-loss outcomes across cortico-striato-limbic regions, consistent with heightened processing of aversive outcomes in depression. Ketamine's attenuation of loss-related signals suggests a change in how outcomes are taken into account during learning, with non-aversive outcomes playing a larger role in shaping expectations.

Salience recalibration and anterior insula prediction-error signalling

Ketamine was associated with enhanced coupling between loss-domain prediction errors and anterior insula activity. Loss prediction errors were coded such that positive values reflected better-than-expected outcomes corresponding to avoidance of loss. Increased insula tracking of these signals under ketamine therefore suggests greater sensitivity to unexpected relief (no-loss), rather than increased loss processing. The anterior insula is a core region within the salience network and has been implicated in aversive learning, uncertainty, and the detection of behaviourally relevant events (Haruno & Kawato, 2006; Menon & Uddin, 2010).

From a cognitive perspective, depression may involve strongly held negative expectations that limit updating from experiences that are better than expected. Increased insula responses to relief-

related (no-loss) prediction errors under ketamine may therefore reflect a loosening of rigid expectations, through greater salience assigned to safety signals during learning. This interpretation is consistent with predictive-processing accounts emphasising altered precision-weighting of affectively relevant information in depression (Adams et al., 2013; Corlett et al., 2016; Gilbert et al., 2022; Kube et al., 2020). The insular, rather than striatal effects may reflect early modulation of salience and interoceptive processing, with downstream changes in learning and behaviour emerging over time.

Selective modulation of outcome evaluation rather than anticipatory processing

A notable distinction in Study 2 was the presence of significant ketamine-related effects during outcome processing in the absence of significant group differences during the anticipatory phases. The task design and the component processes involved in reward-guided behaviour provide a useful way of interpreting this pattern. Anticipation and outcome evaluation represent partially distinct stages of reward processing, with anticipation primarily reflecting the generation of outcome predictions or expectancies, and outcome evaluation involving the encoding of received outcomes and the updating of value representations based on feedback.

In the PILT used in this study, anticipatory value is not explicitly cued but must be inferred gradually through experience with probabilistic contingencies. Unlike tasks with explicit predictive cues (e.g., the Monetary Incentive Delay task), anticipation in this task is implicit and distributed across symbol representations. As a result, anticipatory signals may be weaker, more variable, and less temporally focal, potentially reducing sensitivity to acute pharmacological modulation, particularly in medicated individuals with TRD.

Within this context, the finding that ketamine altered neural responses during outcome evaluation, but not during anticipation, suggests that the PILT is more sensitive to modulation of feedback

processing than to changes in reward and loss anticipation. The absence of anticipatory effects should therefore not be interpreted as evidence against ketamine's impact on reward-related processing, but rather as reflecting the differential engagement and sensitivity of task components. Therefore, these results indicate that outcome evaluation is a particularly robust and detectable stage of reward processing in this paradigm, making it well suited for probing treatment-related changes in feedback-based learning.

Neural modulation in the absence of behavioural change

Ketamine-related neural effects were observed in the absence of group differences in behavioural performance or reinforcement learning parameters. This pattern suggests that ketamine alters neural representations of outcomes prior to corresponding changes in decision policies or clinical symptoms. Neural representations of outcome salience may change rapidly following glutamate-dependent plasticity, whereas stable shifts in choice behaviour in a probabilistic task may require more experience with the environment, particularly in treatment-resistant depression where behavioural change might emerge more slowly.

Ketamine and effort-based decision-making

Effort-based decision-making assessed using the Apples Gathering Task (AGT) showed no clear acute effects at 30 minutes post-infusion, although there was trend-level evidence for a reward x group interaction at this timepoint, indicating possible differences in reward sensitivity between groups. In contrast, a significant reward x group interaction was observed at 7 days, indicating that reward sensitivity differed between the ketamine and placebo groups at follow-up. Specifically, ketamine participants showed reduced reward sensitivity, reflected in smaller increases in acceptance as reward increased and fewer accepted high-reward offers compared with placebo participants. This difference was most evident at mid-range to high reward levels (levels 3–5),

where placebo participants showed greater increases in acceptance with increasing reward magnitude.

Importantly, these effects were not driven by differences in overall acceptance rates, but by differences in the effect of reward magnitude on acceptance behaviour. This indicates that ketamine altered reward sensitivity rather than overall willingness to exert effort, consistent with differences in how reward information influenced value-based decision-making rather than a general increase in motivation. Taken together, this pattern supports the interpretation that ketamine altered reward sensitivity during effort-based decision-making, with behavioural differences emerging in a selective and time-dependent manner.

The delayed group difference in reward sensitivity observed in the AGT is consistent with the neural findings from Study 2, which showed increased insula tracking of relief-related prediction errors under ketamine. The anterior insula has been implicated in signalling the salience and relevance of outcomes for updating value representations, and altered sensitivity to outcome information may therefore influence valuation in situations where reward magnitude must be weighed against effort cost. These findings suggest that ketamine altered how outcome information influenced value-based decision-making.

Reaction time on the AGT provided a complementary measure of reward-related behavioural responding. Increasing reward reduced reaction times overall, consistent with greater behavioural engagement for higher-value offers. At 30 minutes post-infusion, there was a reward x group interaction, indicating that reward had a greater effect on reaction time in the ketamine group compared with placebo participants. Specifically, ketamine participants showed greater reward-related speeding of responses, reflected in a larger reduction in reaction time as reward increased. This indicates that ketamine altered reward-related modulation of response speed shortly after

infusion. However, this group difference was not evident at follow-up, indicating that ketamine and placebo participants did not differ in reward-related modulation of reaction time at 7 days.

Interpreting Symptom Change: Placebo Effects and Timing of Assessment

An important theme across this thesis is the distinction between neural, behavioural, and symptom-level change following treatment. This was particularly evident for ketamine, which has been widely reported to produce rapid antidepressant effects on questionnaire-based measures. In the present study, clinician-rated (HAM-D) and self-reported (QIDS) scores did not demonstrate a clear ketamine-specific improvement at 24 hours post-infusion. Although all symptom measures were analysed using group x time models, a significant interaction emerged only for QIDS, indicating a greater reduction in depressive symptoms over time in the ketamine group relative to placebo.

Several factors may explain this pattern. First, there was substantial improvement in the placebo group at 24 hours, which reduced the ability to detect ketamine-specific effects. Both groups completed five study visits and had regular contact with clinical and research staff. Participation in a closely monitored clinical study can itself be associated with symptom improvement, through increased support, repeated assessment, and the expectation of benefit. If these influences produced early improvement in both groups, the resulting placebo response would reduce the observable difference between ketamine and placebo.

The timing of symptom assessment may also be important. Many ketamine studies report changes in mood within hours of administration. As the earliest post-infusion assessment in the present study occurred at 24 hours, early and potentially transient effects may not have been captured.

The use of a treatment-resistant depression (TRD) sample receiving ongoing antidepressant medication may have further contributed to variability in symptom outcomes. Studies of ketamine frequently exclude medicated participants due to concerns about confounding pharmacological effects; however, the present approach was chosen to provide a more clinically representative sample of individuals typically treated in ketamine clinics. While this increases ecological validity, it may also reduce sensitivity to detect ketamine-specific symptom changes. Future studies could benefit from directly comparing medicated and unmedicated TRD samples to assess whether symptom trajectories and cognitive effects differ across these contexts.

Symptom measures such as the HAM-D and QIDS capture broad depressive symptomatology and are not designed to capture specific alterations in reward or loss processing. Consistent with this, no significant improvements were observed on the TEPS relative to placebo, despite ketamine-related neural effects on outcome evaluation and prediction-error processing. This difference raises the possibility that neural and computational measures may be more sensitive to early treatment-related changes than symptom ratings, particularly in the presence of strong expectancy effects.

Overall, the present findings support the interpretation that ketamine initially alters how outcomes, particularly negative outcomes and safety (no-loss) signals, are evaluated and weighted, with downstream effects on mood and clinical symptoms emerging later and variably captured by self-report and clinician-rated measures. Future studies may therefore benefit from earlier post-infusion symptom assessment and improved strategies for mitigating placebo effects, particularly when using self-report outcomes.

Implications for models of ketamine's antidepressant action

In light of the present findings, ketamine's rapid antidepressant effects appear to involve changes in how feedback is evaluated, rather than immediate effects on reward learning, motivation, or instrumental behaviour. Ketamine was associated with reduced neural responses to loss outcomes alongside relatively greater responses to relief and non-aversive outcomes. This pattern suggests a shift in the balance of outcome evaluation, such that negative outcomes are attenuated during feedback processing, while signals of safety or better-than-expected outcomes are given greater weight.

The findings can also be considered in relation to cognitive neuropsychological models of antidepressant action, which propose that early treatment effects reflect changes in the processing of emotionally salient information rather than immediate alterations in behaviour or learning performance. Within this framework, rapid-acting antidepressants such as ketamine have been hypothesised to reduce the influence of pre-existing negative associations, producing early shifts in affective processing that may precede broader changes in behaviour or clinical symptoms. From this perspective, the pattern of altered neural responses to outcomes observed here may reflect modulation of affective evaluation processes that operate on established expectations, rather than changes in the acquisition of new value representations.

From a clinical perspective, these changes may be experienced as negative events carrying less weight, such that setbacks feel less overwhelming and are less likely to trigger escalating emotional distress. At the same time, successfully avoiding an expected negative outcome may feel more salient or meaningful, with clearer differentiation between positive and negative experiences. These findings provide a neurocognitive account of proposals that ketamine alters maladaptive affective learning processes that maintain negative expectations, without implying direct changes to belief content.

Conventional and rapid-acting antidepressants and loss-related processing

Conventional antidepressant use was associated with differences in how negative outcomes were learned and updated over time, characterised by increased responsiveness to negative feedback while reducing the extent to which learned information is translated into stable choice behaviour, as reflected in lower inverse temperature.

In contrast, ketamine primarily modulated neural outcome evaluation, reducing the relative weighting of loss signals and increasing sensitivity to safety (no-loss) outcomes in aversive contexts. Subtle changes in valuation also emerged during decisions involving mid-range rewards, although these effects were in the opposite direction to the original hypothesis.

Given that these findings arise from studies using different methodologies, and that ketamine was not associated with measurable behavioural changes in this task, direct comparisons should be interpreted cautiously. Nevertheless, the pattern raises the possibility that conventional antidepressant use and ketamine may be associated with different components of loss-related processing. On this account, depressive symptom severity may constrain learning flexibility, conventional antidepressant use was associated with differences in learning dynamics and choice stability, and ketamine may alter the relative salience of outcome information during evaluation, increasing neural differentiation between rewarding and aversive outcomes.

Such an account remains speculative, but it offers a parsimonious framework for understanding how ketamine might contribute to clinical improvement even when reward-related behaviour and self-reported anhedonia remain unchanged at early time points.

Future directions: development of mechanistically informed and clinically accessible tools

The present findings of this thesis highlight a broader challenge for translational psychiatry, namely how to capture mechanistic change in a manner that is both scientifically meaningful and clinically usable. Across studies, alterations in outcome evaluation, loss processing, and learning dynamics were observed in the absence of immediate changes, or in some cases any changes, in self-reported symptoms.

Although neuroimaging and computational modelling were central to the research presented here, such approaches are unlikely to be implemented routinely in clinical practice. At the same time, symptom-based measures provide limited resolution for determining whether a treatment has engaged its hypothesised neurocognitive target, particularly at early time points or in the context of substantial placebo effects. These considerations motivate the development of mechanistically grounded behavioural tools that are accessible and low burden, with a focus on test-retest reliability for use beyond specialised research settings.

The present work also highlights important task considerations. While the PILT was effective in probing outcome evaluation and prediction-error signalling, it may have been less sensitive to anticipatory aspects of reward processing in this medicated treatment-resistant sample. The use of computational modelling increased sensitivity to subtle learning-related effects within the task; however, alternative paradigms may offer improved sensitivity to changes in reward expectation and flexible updating.

In the PILT, stimulus-outcome contingencies remain stable across the task, allowing participants to gradually learn reward probabilities and form relatively consistent value estimates. In contrast, probabilistic reversal learning paradigms introduce changes in contingencies, requiring participants to detect shifts in reinforcement and adjust previously learned responses. This places greater

demands on behavioural flexibility and ongoing value updating. Reversal tasks have shown sensitivity to dopaminergic modulation and to reinforcement learning differences in depression (Mukherjee et al., 2020; Robinson et al., 2012). Incorporating more rapid reversal designs may therefore enhance detection of treatment-related changes in reward expectation and updating dynamics in future studies.

Building on the findings of the thesis, repeated assessment of outcome evaluation, sensitivity to aversive and non-aversive feedback, and the stability with which learned values guide behaviour may provide particularly informative indices of early treatment engagement and recovery trajectory, complementing symptom-based ratings. These components were selectively altered across studies, often in the absence of immediate symptom change, suggesting that they may capture mechanistic effects that precede or unfold independently of subjective improvement.

Such assessments could be administered within clinical settings and or remotely in everyday environments, allowing individuals to continue their usual activities while components of reward processing are assessed using tasks. This approach offers the potential for more personalised and ecologically valid measurement, with mechanistic measures monitored longitudinally across recovery and communicated to clinicians. In turn, these data could inform more targeted psychological interventions tailored to the specific reward-processing components that remain impaired.

Importantly, this proposal does not imply that mechanistic measures should replace clinical assessment. Rather, they may serve as adjunctive tools that help interpret why a given treatment is effective, partially effective, or ineffective for an individual patient. However, substantial challenges remain. Work in cognitive and computational psychiatry has highlighted variability in the reliability of task-derived parameters and the need for careful validation at the individual level

(Enkavi et al., 2019; Haines et al., 2020; Hedge et al., 2018). Future development will therefore need to prioritise robustness, interpretability, and sensitivity to change over time, rather than increasing model complexity.

By grounding tool development in clearly specified neurocognitive mechanisms and targeting the specific evaluative and learning processes modulated by treatment, this approach offers a feasible route to bridging research and clinical care, supporting a shift beyond symptom-centred evaluation toward a comprehensive understanding of mechanistic change, behaviour, and clinical outcome.

Conclusions

This thesis provides new mechanistic insight into how ketamine exerts antidepressant effects, demonstrating that its impact on reward and loss processing extends beyond global changes in reward sensitivity or motivation. Across behavioural, computational, and neuroimaging measures, ketamine was associated with altered evaluation of outcomes in aversive contexts, characterised by reduced neural responses to losses and increased sensitivity to non-aversive or relief-related outcomes. Importantly, these effects were often observed in the absence of immediate changes in behaviour or self-reported anhedonia, indicating that ketamine engages core evaluative processes before downstream changes become clinically or behaviourally observed.

By contrast, findings from a large observational sample indicated that depressive symptom severity and conventional serotonergic antidepressant use were associated with changes in distinct components of loss-related processing. Greater symptom severity was associated with reduced loss learning, consistent with rigid updating from negative outcomes, while antidepressant use was associated with increased responsiveness to negative feedback alongside reduced stability in translating learned values into choice behaviour. These patterns suggest that depression severity and conventional antidepressants primarily influence learning dynamics over time, whereas

ketamine acts at an earlier stage by reshaping how outcome information is evaluated and prioritised.

Overall, these findings highlight loss processing and outcome evaluation as important dimensions of antidepressant action. They challenge models that conceptualise depression primarily as a disorder of blunted reward responsiveness and instead emphasise the importance of how aversive outcomes and signals of safety are weighted during feedback processing. The selective and time-dependent effects of ketamine, in particular, suggest that changes in outcome evaluation may represent an early and mechanistically informative marker of treatment engagement.

By combining behavioural, computational, and neural measures within a mechanistic framework, this thesis illustrates how different treatments engage distinct stages of reward and loss processing, often before changes are detectable at the level of symptoms. Such an approach provides a foundation for more precise models of antidepressant action and supports the development of clinically accessible tools capable of tracking mechanistic change over time. While depression remains a heterogeneous and disabling disorder, focusing on how treatments modify evaluative and learning processes offers a promising route toward more targeted and personalised interventions.

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