Reward Processing and Anhedonia

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Abstract

Anhedonia – a diminished interest or pleasure in activities - is a core self-reported symptom of depression which is poorly understood and often resistant to conventional treatments. Advances in preclinical neuroscience suggest that anhedonia may be due to impairments in one or more sub-components of reward processing: motivation, sensitivity and/or learning. However, the precise deficits remain elusive. This thesis contributes to understanding the relationship between anhedonia and reward-related behaviour by (1) developing novel methods to assess sub-components of reward processing and (2) examining multiple aspects of reward processing using a battery of behavioural tasks in a non-clinical population with higher levels of anhedonia and in a depressed population.

We provide proof-of-concept for two new behavioural paradigms designed to assess: reward motivation (physical effort exerted for reward: Joystick-Operated Runway Task; JORT) and reward learning and memory (based on a procedurally similar rodent task). Using a battery of tasks based on rodent assays, we found evidence that different components of reward may also be dissociable in humans. In a non-clinical population, higher levels of anhedonia were associated with reduced sensitivity to detect reward (Sweet Taste Test) and aberrant effort-based decision-making (Effort Expenditure for Rewards Task). Interestingly, people who had reduced sensitivity did not also display aberrant effort-based decision-making lending support for the presence of sub-groups. We did not find evidence of reduced motivation on a simple effort-for-reward task (JORT). In the depressed population, we did not find clear evidence of dysfunctional reward processing on any paradigms. However, this study is a preliminary study (due to COVID-19) and requires further follow-up before strong conclusions can be drawn.

In summary, our findings support the hypothesis that anhedonia is a heterogeneous symptom. Going forward, there is a critical need for the development and validation of novel translational assays and for further probing of anhedonia in clinical populations.

Dedication

To Harry Benjamin, you were a wonderful kind-hearted person and a special friend.

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Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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Abbreviations

AES	Apathy Evaluation Scale
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BIS/BAS	Behavioural Inhibition System/Behavioural Activation System
CAB	Cognitive Affective Bias
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CPAS	Chapman Physical Anhedonia Scale
CSAS	Chapman Social Anhedonia Scale
Depression	Major Depressive Disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEfRT	Effort Expenditure for Rewards Task
EMA	Ecological Momentary Assessment
FCPS	Fawcett-Clark Pleasure Scale
fMRI	Functional Magnetic Resonance Imaging
GAD-7	Generalised Anxiety Disorder-7
GEE	Generalised Estimating Equation
ICD	International Classification of Diseases
JORT	Joystick-Operated Reward Runway Task
MDD	Major Depressive Disorder
M.I.N.I	Mini International Neuropsychiatric Interview
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health
OSF	Open Science Framework
PRT	Progressive Ratio Task
PSST	Probabilistic Stimulus Selection Task
RBPRT	Response Bias Probabilistic Reward Task
RDoC	Research Domain Criteria
RLA	Reward Learning Assay
SD	Standard Deviation
SHAPS	Snaith-Hamilton Pleasure Scale
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitors
TEPS	Temporal Experience of Pleasure Scale
WHO	World Health Organization

Glossary of key terms

Term	Description
Anhedonia	"Markedly diminished interest or pleasure in all, or almost all, activities" (American Psychiatric Association, 2013).
Mini-International Neuropsychiatric Interview (*M.I.N.I.;* Sheehan et al., 1998)	A brief neuropsychiatric diagnostic interview for DSM and ICD psychiatric disorders.
National Institute of Mental Health (*NIMH*)	Organisation dedicated to research into mental illnesses, which is part of the National Institute of Health in the United States.
National Institute for Health and Care Excellence (*NICE*) guidelines	Evidence-based recommendations for health and social care in England.
Open Science Framework (*OSF*)	Free online tool (by Centre for Open Science) that encourages open dissemination of research: researchers can upload and share pre-registrations of studies, papers and preprints, study data and code.
Preclinical research	Research conducted prior to human work. Here, it specifically refers to animal research - typically conducted with rodents.
Prolific Academic	An online platform for recruiting participants to studies (prolific.co). Currently, enables access to more than 70,000 participants worldwide.
Research Domain Criteria (*RDoC*)	Research framework proposed by the NIMH to classify and investigate mental illness. Encourages researchers to take a dimensional approach (i.e., not to focus on diagnostic categories) and to integrate across methods (e.g., self-report, behaviour, brain imaging).
Translational research	Research that can be conducted across species (animals and humans). Aims to promote findings from animal research to inform human research.

Chapter 1: General Introduction

1.1. Overview

In this thesis, I examine how anhedonia relates to behavioural measures of reward processing, with a particular focus on translational paradigms. In this general introduction, I will briefly discuss Major Depressive Disorder (the context in which anhedonia has mostly been studied due to its high prevalence and severity in this disorder), how anhedonia has traditionally been measured (using subjective questionnaires) and recent attempts to understand anhedonia using objective translational measures of reward processing. Following this, I will conclude with some gaps in the current literature, and how this thesis will contribute to these gaps.

1.2. Major Depressive Disorder

1.2.1. Diagnostic criteria

Worldwide, mental health disorders are diagnosed based on a constellation of self-reported symptoms present over a defined period of time (American Psychiatric Association, 2013; World Health Organization., 2018). The two most commonly used classification systems for diagnosing mental health conditions are the *International Classification of Diseases* (ICD; World Health Organization., 2018) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; American Psychiatric Association, 2013). Whilst the ICD is used internationally to classify a range of health disorders, the DSM is specific to psychiatric disorders and is predominantly used for research and clinical practice in the United States (Clark et al., 2017). These diagnostic manuals are not finished products; new editions are released over time that aim to reflect advances in research. However, for most disorders, including major depressive disorder (*herein referred to as depression*), there are few changes to criteria across editions (Cooper, 2018; Regier et al., 2013).

The diagnostic criteria for a major depressive episode (MDE) using the latest versions of the ICD (ICD-11) and the DSM (DSM-5) are similar. For a diagnosis, an individual must report experiencing one of the two core

symptoms (depressed mood and/or anhedonia) alongside other symptoms (e.g., fatigue, sleep disturbances) nearly every day, for a period of at least 2-weeks (American Psychiatric Association, 2013). In total, the individual must report at least five symptoms (see Table 1.1). The main difference between the two systems in the diagnosis of a MDE is that the (1) the ICD-11 includes ten possible symptoms whereas the DSM-5 includes nine (hopelessness being the additional symptom in the ICD-11) and (2) the ICD-11 includes a "bereavement exclusion" which is no longer present in the DSM-5 (Stein et al., 2020). In the DSM-5, hopelessness was introduced but within the criterion of depressed mood (see Table 1.1) and the bereavement exclusion was replaced by a note stating that clinical judgement is required when diagnosing MDE following significant loss (Uher et al., 2014). Depression can also be characterised by its severity which can be mild, moderate or severe (Beck et al., 1996).

Table 1.1 DSM-5 criteria for a Major Depressive Episode (adapted from American Psychiatric Association, 2013)

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) anhedonia.
1. Depressed mood Most of the day, nearly every day as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).
2. Anhedonia Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Weight loss or gain Significant weight loss when not dieting or weight gain (e.g., a change of > 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia or hyposomnia Nearly every day.
5. Psychomotor agitation or retardation Nearly every day.
6. Fatigue or loss of energy Nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt Nearly every day; guilt may be delusional.
8. Decreased concentration Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or observed by others).
9. Thoughts of death/suicide Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
Additional requirements: (1) Symptoms must cause clinically significant distress or impairment in social, occupational or other important areas of functioning, (2) episode not attributable to physiological effects of a substance or another medical condition, (3) episode not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other schizophrenia spectrum and other psychotic disorders and (4) there has never been a manic episode or a hypomanic episode.

Please see the DSM-5 manual for precise wording and notes (American Psychiatric Association, 2013).

1.2.2. Prevalence and importance

Depression is a debilitating and often recurrent mental illness, affecting approximately 300 million people worldwide (~ 4.4% population)(WHO, 2017). In England, the estimated 12-month prevalence rate of depression is 3.3% or 7.8% when including people with mixed-depression and anxiety (McManus et al., 2009). In terms of lifetime prevalence in England, depression is the most frequently diagnosed mental illness, with approximately 19% of adults (13% men, 24% women) reporting that they had received a diagnosis of depression at some point during their life (2014 Health Survey for England; Bridges, 2014). It is important to note that these surveys are sent to private houses in England (i.e., they are not distributed in hospitals, prisons, sheltered housing or to the homeless), and thus it is possible that the prevalence of depression is higher. Whilst prevalence estimates across countries have been shown to vary considerably (Kessler et al., 2003; Kessler & Bromet, 2013), a consistent finding across countries is that women have a higher risk of depression compared to men (Kessler & Bromet, 2013).

The high prevalence of depression is very concerning, especially when taking into consideration its enormous impact on the individual, society and the economy. Depression significantly affects a person's quality of life and is associated with a higher risk of early death. For example, depression is associated with an increased risk of suicide (Beautrais, 2000). In the UK, suicide is the leading cause of death for both males and females between the ages of 5 to 34 (Office for National Statistics, 2019). Not only does depression increase a person's risk of suicide (Bachmann, 2018), it is also associated with a higher risk of a wide range of physical disorders when compared to healthy controls (Farmer et al., 2008) including hypertension (odds ratio: 2.20), gastric ulcer (odds ratio: 4.31), type 2 diabetes (odds ratio: 2.06) and myocardial infarction (odds ratio: 2.70; as reported in Farmer et al., 2008), which in turn are associated with an increased risk of mortality (Abbafati et al., 2020). Furthermore, in England (2007) the estimated yearly service cost for depression was £1.7 billion, which increased to £7.5 billion when including lost earnings

(Mccrone et al., 2008). The high prevalence of depression and its huge impact on society has made understanding depression and its treatment a major public health priority (World Health Organization, 2020).

1.2.3. Treatments for depression

The most commonly offered treatments for depression are psychological therapy and/or antidepressants. Based on the current National Institute for Health and Care Excellence guidelines (NICE, 2009), the recommended treatment for an individual varies depending on the severity of their depression. For mild-to-moderate depression, low-intensity psychosocial interventions (supported self-help), physical activity and/or computerised cognitive behavioural therapy (CBT) are recommended (NICE, 2009). Whereas, for moderate-to-severe depression, a first-line antidepressant (e.g., selective serotonin reuptake inhibitor; SSRI such as citalopram, sertraline) combined with a high intensity psychological therapy (e.g., individual CBT, behavioural activation therapy) is recommended (NICE, 2009). If there is little response following an SSRI, the clinician may propose that the patient try a higher dose of the current SSRI, a different SSRI or a different class of antidepressants (e.g., serotonin and norepinephrine reuptake inhibitor, tricyclic antidepressant or monoamine oxidase inhibitor)(NICE, 2009). In the case of treatment-resistant patients, brain stimulation such as electroconvulsive therapy (ECT) may be offered (NICE, 2009). Alternative treatments not included in the guidelines (but approved by NICE) are repeated transcranial magnetic stimulation and vagus nerve stimulation (NICE, 2015, 2020b). Despite the range of available treatments for depression, it is important to note that the precise therapeutic mechanisms of action for available treatments remains poorly understood and commonly prescribed antidepressants were discovered serendipitously (Robinson, 2018).

There are also other promising treatment options emerging for treatment-resistant depression, but these are not currently recommended by NICE (NICE, 2009). First, there is some evidence that deep brain

stimulation (DBS; electrodes implanted into the brain to deliver electrical stimulation) in regions such as the nucleus accumbens and subcallosal cingulate reduce symptoms of depression (Bewernick et al., 2010; Mayberg et al., 2005). More recently, studies have shown that ketamine reduces symptoms of depression within hours and has lasting effects in treatment-resistant patients (Murrough et al., 2013). Whilst esketamine (isomer of ketamine) has been approved for licensing in the United States for treatment-resistant depression, it is not currently recommended by NICE (NICE, 2009). The reason why these treatments are not currently recommended by NICE is because of limited evidence on their efficacy, safety and/or cost-effectiveness (NICE, 2020a).

Whilst there are effective treatments available for depression, there are problems with current interventions. Firstly, current pharmacological and psychological treatments are not effective for many people. For example, up to ~ 50% people do not fully respond (defined as ≥ 50% symptom reduction) to conventional antidepressants (Fava & Davidson, 1996). A naturalistic study of nearly 3,000 patients with depression reported that only ~30% patients achieved remission (near absence of symptoms) following an SSRI treatment of citalopram (47% responded in total; Trivedi et al., 2006). Moreover, for moderate-to-severe depression, both cognitive therapy and antidepressants show limited efficacy in terms of response rate (43% and 50%) and remission rates (40% and 46%; DeRubeis et al., 2005). Secondly, even when people do respond or show remission of symptoms, there is a high risk of relapse and recurrence (DeRubeis et al., 2008; Vitiello et al., 2011). This suggests that available treatments may help in suppressing, but not curing symptoms (DeRubeis et al., 2008). Thirdly, conventional antidepressants have been reported to have a delayed onset of action (Godlewska & Harmer, 2020; Harmer & Cowen, 2013). This means that it can take several weeks (~ 4 – 6 weeks) after treatment onset before patients report a *clear* alleviation of their symptoms (Frazer & Benmansour, 2002; Taylor et al., 2006). As finding an effective treatment for an individual usually takes trial-and-error of several treatments (Cuijpers et al., 2020), this is time-consuming, discouraging for patients, and costly for society. Finally, conventional

antidepressants can have a range of side effects including sexual dysfunction, gastrointestinal disturbance, emotional blunting (Robinson, 2018), and increase suicide risk during early treatment (Healy & Whitaker, 2003). Therefore, although conventional antidepressants are effective for some individuals, the poor treatment response, delayed onset of action and side effects emphasize the need for new effective treatments.

Pharmaceutical companies have invested heavily in the development of effective novel treatments with limited success (Belzung, 2014). Several factors have contributed to this failure, a chief one being a poor mechanistic understanding of depression. It is likely that the development of better treatments will require insight into the mechanisms underpinning this disorder.

1.2.4. Causes of depression (the '*why*' and the '*how*')

In the last 50 years, a significant amount of research has sought to identify the causes and development of depression. As it is not the focus of this thesis, it is only briefly mentioned here.

Despite earlier nature-versus-nurture debates, it is now widely thought that depression is caused by both genetic and environmental factors. For example, a meta-analysis of five twin studies reported the heritability of depression to be 37% (Sullivan et al., 2000), leaving 63% attributable to an individual's environment. The diathesis-stress model tries to account for this complexity, proposing that depression is the result of a complex interaction between vulnerability factors during early development (such as genetics, early life stress) and stressful life events (such as divorce, job loss, infection)(Robins & Block, 1989). The complex interaction between these genetic and environmental factors result in neurobiological and psychological changes, which are thought to be involved in the development and maintenance of depression.

In terms of the development and maintenance of depression, a number of neurobiological theories of depression have been proposed. Arguably, the most widely researched neurobiological theory is the monoamine hypothesis, which associates depression with a depletion of neurotransmitters in the central nervous system (e.g., serotonin, norepinephrine and dopamine; see Willner et al., 2013). Whilst there is evidence in support of this theory, the delayed onset of action of drugs which enhance monoamine levels (Harmer & Cowen, 2013; Taylor et al., 2006) and their failure to alleviate symptoms in many patients (Fava & Davidson, 1996) has led some researchers to consider other theories.

More recently, other neurobiological theories have been proposed such as altered stress response and the hypothalamic-pituitary-adrenal axis, neurocircuitry changes, neurotrophic deficits associated with neuron, dendrite and/or synapse loss, altered circadian rhythms, inflammation and vitamin D deficiency (for reviews see Hasler, 2010 and Jesulola et al., 2018). It is important to note that most work investigating the neurobiological mechanisms of depression, particularly within animal research, has focused on antidepressant mechanisms (Rot et al., 2009), despite the fact that conventional antidepressants often supress (as opposed to cure) symptoms and are not effective for many people with depression (DeRubeis et al., 2005, 2008; Fava & Davidson, 1996).

Cognitive theories of depression have also been proposed to play a key role in the development and maintenance of depression. Prominent psychological theories of depression include cognitive affective biases (CAB) and dysfunctional reward processing (Admon & Pizzagalli, 2015; Eshel & Roiser, 2010; Robinson et al., 2016). The CAB theory, based on earlier work by Aaron Beck (Beck, 1979), proposes that people with depression exhibit negative biases in their attention, memory and interpretation of ambiguous information (Gotlib & Joormann, 2010). Dysfunctional reward processing is also gaining traction as a promising potential mechanism involved in the development of depression (Halahakoon et al., 2020; Nielson et al., 2020). Overall, whilst often discussed as competing theories, these theories are not likely to be

mutually exclusive, instead they likely interact with each other in the development of depression.

Nevertheless, these theories face several challenges. This includes the problem of inferring causality and the problem of heterogeneity. One challenge has been the difficulty in discerning whether factors are causal, correlates or consequences of depression (Nielson et al., 2020). To address this question, longitudinal data is required to examine depression over time. An additional challenge is the considerable heterogeneity present in depression (discussed in more detail in section 1.2.5). For example, whilst there is increasing support for the *causal* role of inflammation in depression (Osimo et al., 2020), only around 25-50% of patients with depression have elevated, or persistently low, levels of inflammation (Osimo et al., 2019). Therefore, whilst inflammation appears to play an important *causal* role in depression, this may only be the case for a sub-group of patients.

1.2.5. Heterogeneity problem: moving away from traditional diagnostic criteria

As just mentioned, a critical and widely recognised problem in the research and treatment of depression is its heterogeneity. The vast majority of depression research focuses on clinical diagnostic categories (DSM-5, ICD-11), posing questions such as "what are the biomarkers of depression" or "what treatments are effective for depression?" (Fried & Nesse, 2015). These questions are all based on the underlying notion that depression is a unitary homogeneous disorder (Fried & Nesse, 2015). However, people with the same diagnosis of depression can vary considerably in their aetiology, symptom profile, comorbidity (presence of co-occurring disorders) and treatment response (Treadway & Zald, 2011). For example, two people can have the same diagnosis of depression whilst only having one symptom in common (Treadway & Zald, 2011). This is not surprising considering that there are apparently 227 different ways in which a person could meet criteria for depression (Zimmerman et al., 2015). This large heterogeneity and the limited progress in

depression research have led many to reconsider the view that depression is a single condition:

> ***"To declare that all those satisfying the DSM criteria for the diagnosis of major depression are suffering from the same disorder seems like magical thinking… It may be politically important to utter such simplifications to doctors in general medical setting, but it is a convenient fiction (Goldberg, 2011)"***

Consequently, if depression is not a single unitary condition, research relying solely on diagnostic categories may obscure insights and hinder progress (Fried & Nesse, 2015). This is crucial because a biomarker or treatment, which may be relevant and effective for a sub-group of individuals, may be masked when examined in a large heterogeneous group. Unfortunately, despite awareness that depression is unlikely to be a single entity, it has been difficult for researchers to move away from using diagnostic categories for various reasons (e.g., required use in funding applications and the lack of a clear alternative approach; Clark et al., 2017).

To address this limitation in research, the National Institute of Mental Health (NIMH) introduced the Research Domain Criteria project in 2009 (RDoC; Insel et al., 2010). In brief, the RDoC proposes a new approach to classifying mental illnesses in research, encouraging researchers to move away from traditional diagnostic categories (DSM/ICD) to a dimensional approach focusing on psychological processes or symptoms (Clark et al., 2017; Cuthbert, 2014). As a starting point, it proposed five research domains of human functioning (positive valence, negative valence, cognitive systems, social processes, arousal systems; see Cuthbert 2014 for more details), which has since been expanded to six domains (sensorimotor systems being the additional domain). Using these six domains, it aims to integrate research across multiple levels of analysis (e.g., self-report, behaviour, physiology, neural circuits, cells, molecules and genes; Dillon et al., 2014). Focusing on symptoms or psychological processes, as opposed to heterogeneous clinical disorders,

may aid the development of targeted treatments. This is because unlike diverse clinical groups, a psychological process (or symptom) is more likely to have a distinct behavioural and neurobiological basis that can be targeted by treatments (Thomsen et al., 2015). One crucial symptom, which is thought to be closely aligned with the positive valence domain and is often neglected by current treatments, is anhedonia (Cuthbert, 2014; McMakin et al., 2012; Uher et al., 2012).

1.3. Anhedonia

1.3.1. What is anhedonia?

The word *anhedonia* was created in 1896 by the French psychologist Théodule-Armand Ribot. It was defined as a "loss of pleasure", deriving from the Greek words "an-" (without) and "hedone" (pleasure). Ribot invented this term to name a condition observed in psychiatric patients: *"She…would play with her doll but could not be brought to show any delight in it; could not be drawn out of her apathetic sadness. Things which previously made her shriek with laughter now left her uninterested"* (as reported in Snaith et al., 1995). Since then, psychologists have continued to use this term to refer to the symptom reported by patients with mental health conditions, particularly depression.

However, it is now recognised that the original definition of anhedonia (*loss of pleasure*) may not accurately reflect this condition (Husain & Roiser, 2018). For example, it is rare for people to show a complete absence of pleasure (Snaith et al., 1995). Instead, most people with anhedonia show reduced pleasure but may still attain pleasure from a limited number of sources (Ho & Sommers, 2013; Meehl, 1990; Snaith et al., 1995). More importantly, it became apparent that a broader deficit may be present in these patients (Snaith et al., 1995). For example, people with anhedonia may experience deficits in consummatory pleasure (pleasure experienced in the present) and/or deficits in their anticipatory pleasure (pleasure derived from anticipating future events; Klein, 1974).

In the diagnostic manuals, the word "anhedonia" is not used but this condition is acknowledged as a symptom of many disorders including depression and schizophrenia. For example, it is a cardinal symptom of depression defined as a "markedly diminished interest or pleasure, in all, or almost all, activities most of the day nearly every day" (DSM-5; American Psychiatric Association, 2013). This diagnostic definition also acknowledges that broader pleasure impairments may be experienced by depressed patients. Throughout this thesis, the word "anhedonia" refers to this broad *self-reported condition* (i.e., not the original definition restricted to the loss of pleasure).

1.3.2. Reconceptualization of anhedonia

The definition and concept of anhedonia is widely debated and still evolving within the research literature. In particular, progress in affective neuroscience has led to an expansion in the definition and conceptualisation of anhedonia. Two definitions which have been proposed within the field are those of Treadway & Zald (Treadway & Zald, 2011) and Thomsen et al. (Thomsen et al., 2015; see Table 1.2).

An important difference between these definitions is the precise pleasure components proposed to be dysfunctional in people who self-report anhedonia. For example, both suggest that anhedonia may involve motivational and/or consummatory deficits, but differ in their third deficit: a decisional impairment in the Treadway definition and learning impairment in the Thomsen definition. Arguably, addressing which components are relevant to anhedonia will require careful dissection of components (preferably using objective measures) linked to self-reported anhedonia assessments. In this respect, there is a promising literature developing objective measures of reward processing, see section 1.4.5.

A similarity between these definitions is that they both acknowledge the heterogeneity within anhedonia (i.e., the presence of sub-groups; Thomsen et al., 2015; Treadway & Zald, 2011) when considering reward deficits associated with anhedonia. The proposal of sub-groups within

anhedonia is important and could have critical implications for treatment. Specifically, it suggests that whilst patients may appear similar at a self-report symptomatic level, they may differ in their underlying impairments (e.g., some patients may experience impairments in motivation to obtain pleasure whilst others may experience deficits in consummatory pleasure)(Husain & Roiser, 2018). Whilst this is not necessarily a new idea (Klein, 1974), many studies to date have considered anhedonia to be a unitary construct. In my opinion, to address whether self-reported anhedonia is composed of distinct sub-groups, studies will need to demonstrate dissociations between different pleasure components in the same sample of people. For example, a similar approach has been taken in the field of memory: initially, memory was considered to be a single unitary system which was measured using a single task (learning and recalling a list of words or paragraphs of prose; Baddeley, 1984); however, this field has since demonstrated dissociations between different memory components (e.g., episodic versus semantic memory) by careful measurement of these components within the same sample of patients reporting memory deficits (Temple & Richardson, 2004; Vargha-Khadem et al., 1997). Following this example, I think that the definition of anhedonia and its conceptualisation will become clearer as we refine measurements of distinct components of pleasure within the same individuals.

Table 1.2 Proposed definitions of anhedonia, modified from (Slaney et al., 2018)

Dates	Definition	Author
1896	Loss of pleasure	Ribot
1974	Consummatory vs anticipatory anhedonia	Klein
2013	"Markedly diminished interest or pleasure"	DSM-5
2011	Consummatory, motivational and decisional anhedonia	Treadway & Zald
2015	"Impairments in the ability to pursue, experience and/or learn about pleasure, which is often, but not always accessible to conscious awareness"	Thomsen, Whybrow & Kringelbach

As a final remark, it is important to realise that the fractionation of the concept of anhedonia goes beyond the distinction between pleasure components impaired (e.g., consummatory versus anticipatory). Specifically, this fractionation includes the state-versus-trait dichotomy (fluctuating symptom or a stable trait), dimensional versus categorical debate (variable symptom within the normal population or an all-or-nothing clinical condition), domains of pleasure impaired (domain-specific: social versus physical) and its specificity to pleasure (deficit in pleasure or global flattening). For a recent review discussing this evolving conceptualisation, see (De Fruyt et al., 2020).

To summarise, the definition and concept of anhedonia is evolving, particularly in the field of neuroscience. This has led to the proposal of new definitions of anhedonia based on advances in research. In this thesis, the working definition of anhedonia is: diminished self-reported pleasure, which may be driven by reduced appetitive motivation, consummatory experience and/or learning. Here, I focus on anhedonia as the subjective experience, the underlying cause of which may be due to objective changes in the reward system.

1.3.3. Prevalence and importance

Anhedonia is very common in depression. However, its estimated prevalence varies considerably depending on how it is measured (Husain & Roiser, 2018). For example, prevalence estimates of anhedonia within depression are much higher when a single question is used to assess the presence of anhedonia (~ 80 – 90%; Haarasilta et al., 2001; Zimmerman et al., 2015), compared to when anhedonia questionnaires are used (~ 37% based on cut-offs indicating clinically significant levels of anhedonia; Pelizza & Ferrari, 2009). Anhedonia is also common in other conditions such as Schizophrenia (45%; Pelizza & Ferrari, 2009), Parkinson's disease (46%; Lemke et al., 2005) and Alzheimer's (61%; Lopez et al., 2003), as summarised by Husain and Roiser (Husain & Roiser, 2018).

Although anhedonia is prevalent across many disorders, it is reported to be most severe in depression (Trøstheim et al., 2020). For example, a meta-analysis comparing *severity* of anhedonia (using an anhedonia questionnaire) across six disorders (major depression, bipolar disorder, schizophrenia, substance use disorders, Parkinson's disease and chronic pain) found that whilst anhedonia scores were higher in all disorders compared to healthy controls, anhedonia scores in major depression were considerably higher (Trøstheim et al., 2020).

As well as being highly prevalent, anhedonia predicts poor response to antidepressants (McMakin et al., 2012; Uher et al., 2012). For example, in a sample of 811 adults with moderate-to-severe depression, anhedonia (measured as low interest, activity, enjoyment and indecisiveness) strongly predicted poor improvement from antidepressants on multiple depression questionnaires (Uher et al., 2012). Importantly, this prediction was independent of a person's severity of depression, the type of antidepressant used and the outcome measure (Uher et al., 2012). Consequently, there is clearly a critical need for novel treatments targeting anhedonia.

1.3.4. How is anhedonia measured: subjective measures

Traditionally, anhedonia has been assessed using subjective measures such as questionnaires and clinical interviews. In many studies and in clinical practice, anhedonia is measured using a few questions on a depression scale (Beck Depression Inventory-II, Beck et al., 1996)(Treadway & Zald, 2011). However, relying on a few questions to measure a construct such as anhedonia can lead to poor reliability. As a result, several anhedonia questionnaires have been developed. The most widely used anhedonia questionnaires are the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995), Revised Chapman Physical Anhedonia Scale (CPAS; Chapman et al., 1976), Revised Chapman Social Anhedonia Scale (CSAS; Chapman et al., 1976) and the Fawcett-Clark Pleasure Scale (FCPS; Fawcett et al., 1983).

There are similarities across these scales but there are also some important differences. As these scales will be used as self-report measures of anhedonia in this thesis, I will discuss similarities and differences here (see Rizvi et al., 2016 for a detailed review). Broadly, key differences between measures include (1) the disorder it was validated to measure anhedonia in (depression or schizophrenia), (2) conceptualisation of anhedonia (state versus trait, physical versus social, consummatory versus anticipatory), (3) cultural considerations and (4) psychometric properties (as summarised in Rizvi, 2015; Rizvi et al., 2016).

Most anhedonia questionnaires were initially validated in depressed populations (FCPS, SHAPS). In contrast, the Chapman scales were developed for patients with schizophrenia (CPAS, CSAS). Since their initial development, these scales have also been validated in other populations (see Table 1.3). It is important to check the populations in which a scale has been validated in as a failure to do so may reduce the confidence in conclusions and result in measurement error (Dowrick et al., 2015).

These questionnaires also diverge in their conceptualisation of anhedonia. First, they differ in whether they assess anhedonia as a state (a fluctuating symptom: SHAPS, FCPS) or trait (stable construct over time: CPAS; Rizvi, 2015; Rizvi et al., 2016). This is likely based on the different disorders in which these scales were initially developed (with depression often thought to be more episodic in nature). Nevertheless, it is likely that trait anhedonia is reflected at least to some degree in many state measures, as many state questionnaires (including the SHAPS) do not ask participants to compare their current state to a baseline level (Winer et al., 2019). A second consideration is the domain in which anhedonia is experienced (e.g., physical versus social; Rizvi et al., 2016; Winer et al., 2019). The majority of anhedonia scales focus on physical anhedonia (FCPS, SHAPS, CPAS; i.e., deficits in experiencing pleasure from physical activities such as eating). In contrast, the CSAS was designed specifically to measure social anhedonia (i.e., deficits in experiencing pleasure from interpersonal relationships). Finally, most questionnaires focus on

consummatory pleasure (FCPS, SHAPS; Leventhal et al., 2006; Rizvi et al., 2016). This is important as it is now widely recognised that anhedonia may not be specific to deficits in consummatory pleasure (Thomsen et al., 2015; Treadway & Zald, 2011). Whilst some scales do include questions that ask about other pleasure deficits (e.g., motivation and anticipation of future pleasure), they often conflate these into a single summary score.

The scales also vary in their cultural relevance (Leventhal et al., 2006; Rizvi et al., 2016). Unlike the FCPS and CPAS, the SHAPS is more generalisable across cultures (Leventhal et al., 2006; Rizvi et al., 2016). Specifically, the FCPS and CPAS reference pleasurable activities that are either culturally dependent and/or outdated, see Table 1.3 for examples. The outdated nature of the CPAS is not too surprising given that this questionnaire was created in the 1970s.

In terms of validity, two factors are important: convergent and discriminant validity. Convergent validity is how well a measure correlates with other measures attempting to address the same construct. Discriminant validity ensures that a measure does not correlate too highly with other measures that address a different (but often related) construct (Rizvi et al., 2016). For example, anhedonia scales would ideally correlate with each other (at least to some degree), but would not correlate too highly with measures assessing anxiety, depression and apathy (Rizvi, 2015). Broadly, across different studies, these scales have shown at least adequate convergent and discriminant validity (although see Leventhal et al., 2006; Treadway et al., 2009). However, discriminant validity from apathy measures is less clear as few studies have included both in the same population (Husain & Roiser, 2018).

In sum, traditional self-report measures of anhedonia vary across many factors (Rizvi et al., 2016). Whilst they have all demonstrated adequate validity, they have been criticised for being outdated and focusing on consummatory pleasure (Rizvi et al., 2016). In an attempt to address these limitations, new scales have been developed such as the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006). The TEPS consists

of two subscales designed to tease apart consummatory pleasure from anticipatory pleasure. Whilst promising, these scales have not yet been validated to the same degree as traditional questionnaires (Rizvi et al., 2016). Moreover, it is not yet clear whether we can adequately tease apart these different pleasure components using self-report measures (see Garfield et al., 2016).

Table 1.3 Anhedonia questionnaires (modified from Rizvi et al., 2016)

Questionnaires	***Some* populations tested**	**Instruction and response**	**State versus trait**	**Domains of anhedonia** *(consummatory versus anticipatory)*	**Dimension**	**Cultural consideration**	**Length**	**Example items**
Chapman Physical Anhedonia Scale Revised (CPAS)	Depression Schizophrenia Healthy controls Alcohol abuse	Describe yourself as you have been during most of your adult life. Response: true or false	Trait	Both	Physical	Limited	61 items	"I always find organ music dull and unexciting" "I have usually found love making to be intensely pleasurable"
Chapman Social Anhedonia Scale Revised (CSAS)	Depression Schizophrenia Healthy controls Alcohol abuse	Describe yourself as you have been during most of your adult life. Response: true or false	Trait	Both	Social	Good	40 items	"Just being with friends can make me feel really good" "Making new friends isn't worth the energy it takes"
Snaith Hamilton Pleasure Scale (SHAPS)	Depression Schizophrenia Healthy controls Bipolar disorder Substance abuse	How much you agree or disagree with each statement in the last few days. Response: 4-point scale (strongly agree to strongly disagree)	State (last few days)	Consummatory	Both	Good	14 items	"I would enjoy a cup of tea, coffee or my favourite drink" "I would enjoy my favourite television or radio program"
Fawcett Clark Pleasure Scale (FCPS)	Depression Schizophrenia Healthy controls Bipolar disorder	Rate imagined hedonic reactions to hypothetical pleasurable situations Response: 5-point scale (no pleasure at all to extreme and lasting pleasure)	State (right now)	Consummatory (imagined)	Both	Limited	36 items	"You are skiing down a mountain very fast while still in good control of yourself" "You sit watching a beautiful sunset in an isolated, untouched part of the world"
Temporal Experience of Pleasure Scale (TEPS)	Depression Schizophrenia Healthy controls Bipolar disorder Substance abuse	How true that statement is for you in general. Response: 6-point scale (very false for me to very true for me)	Trait	Both (contains sub-scales to dissociate)	Physical	Good	18 items	"The smell of freshly cut grass is enjoyable to me" "I appreciate the beauty of a fresh snowfall"

1.3.5. Limitations of subjective measures

Anhedonia questionnaires provide an important insight into a person's subjective experience, which is crucial in mood disorders. However, there are limitations of over-relying on questionnaires to measure anhedonia, which I will now outline.

Arguably, one of the biggest limitations of self-measures is their failure to provide a mechanistic understanding of a condition. Specifically, they cannot reveal the behavioural, cognitive, or neurobiological dysfunctions that underpin a condition. To make progress in the diagnosis and treatment of many conditions, including anhedonia, it is likely that we will need to look beyond the "surface manifestation" reported by patients (Husain & Roiser, 2018).

Another limitation of anhedonia questionnaires is their reliance on patient insight (Chong et al., 2016) and conscious experience. Some of the impairments underpinning anhedonia may not be consciously accessible (see section 1.4.3; Berridge et al., 2009). Thus, whilst questionnaires may shed light on conscious impairments in anhedonia, they will not provide a full picture of the condition (Thomsen, 2015).

A further limitation of these questionnaires is that they are likely confounded by a person's memory of an event (i.e., recall bias; Solhan et al., 2009; Zald & Treadway, 2017). For example, Ecological Momentary Assessment (EMA) studies, which assess an individual's experience in their natural environment, only moderately correlate with retrospective affective questionnaires (Solhan et al., 2009). This poor retrospective account questions a person's ability to accurately remember their in-the-moment experience of pleasure.

Finally, questionnaires hinder our ability to conduct translational research, as they cannot be applied in animal studies (Aylward et al., 2019). In this thesis, translational research refers to the use of procedurally similar measures that can be applied across species (i.e., in both human and rodent studies). This is a big limitation, as research in rodents is critical for gaining insight into the neurobiology of anhedonia and in the development of effective new drugs (Robinson, 2018). Currently, whilst

rodent studies use objective behavioural tasks to measure anhedonia, human studies still rely on questionnaires (Emslie et al., 2002; Lavretsky et al., 2020; Trivedi et al., 2006). The difference in measurements across species may partly account for the failure to develop effective pharmacological drugs for psychiatric conditions (Aylward et al., 2019; Belzung, 2014). Thus, there is a need for measures that can be used in both preclinical and clinical research to bridge this gap.

In sum, whilst questionnaires provide a valuable insight into a patient's subjective experience, there are several limitations to over-relying on these measures. As a result, there is a need for objective measures that will complement the subjective measures currently used in clinical practice.

1.3.6. The need for objective measures in anhedonia research

Despite the clear importance of anhedonia, the psychological and neurobiological basis of this condition remains poorly understood (J. A. Cooper et al., 2018). This is, at least partly, due to the over-reliance on questionnaires to measure this symptom. In line with the RDoC (see section 1.2.5), there is a need for objective measures to be used alongside self-report measures (Husain & Roiser, 2018). Few studies have attempted to objectively characterize the precise impairments using laboratory-based measures (Pizzagalli et al., 2008). However, there has been an increased interest in this field, with reward processing deficits emerging as a promising mechanism underpinning anhedonia (Halahakoon et al., 2020).

1.4. Reward Processing

1.4.1. Definition of a reward

Broadly, the term "reward" refers to an appetitive stimulus which has the *potential* to get us to approach it (Schultz, 2015). It is important to note that it is not the inherent properties of a stimulus that makes it rewarding, but rather our behavioural response to it (Schultz, 2015). Thus, whilst we group certain stimuli as being "rewards", these are not

static, and their ability to influence our behaviour can vary depending on our internal state and external environment (i.e., they are context dependent; Schultz, 2015). For example, you may seek out and gain pleasure from food when you are hungry, but this may not be the case after a finishing a three-course meal. Thus, whilst rewards have the capacity to drive behaviour and induce pleasure, their ability to do so depends on several internal and external factors (Schultz, 2015).

1.4.2. Types of reward

A common but possibly crude distinction used within the literature is that of primary versus secondary rewards (Lawn, 2016; Rizvi et al., 2016; Sescousse et al., 2013; Wolke, 2018). Primary rewards are innate and critical for survival and procreation (e.g., food, water and sex), whereas secondary rewards are learnt through their association with primary rewards (e.g., money). Nevertheless, there are some rewards that do not neatly fit into these two categories such as music, art and social feedback (Lawn, 2016; Mas-Herrero et al., 2013; Thomsen, 2015).

In human research, the majority of studies use monetary rewards due to it being universally valued and easily manipulated. Moreover, primary rewards (e.g., food), are arguably more variable between individuals (people have preferences for different types of food) and within individuals (dependent upon the physiological state of the individual), making them more challenging to use in human experiments. In contrast, preclinical studies use primary rewards in behavioural tasks such as food or liquids (Berridge & Robinson, 2003). It is unclear whether these different types of rewards are processed similarly in the brain (Sescousse et al., 2013). One meta-analysis reported that whilst primary and secondary rewards engage a common neural system, secondary rewards activate additional regions (Sescousse et al., 2013). Thus, the type of reward is an important consideration for behavioural studies, and in particular cross-species translational research which often use different types of reward.

1.4.3. Reward processing: wanting, liking and learning

Reward processing (i.e., our ability to recognise and engage with rewards in our environment) is vital for our survival, reproduction and well-being. Crucially, reward processing is not a unitary construct (Berridge et al., 2009; Thomsen, 2015). Accumulating evidence suggests that it is composed of at least three different sub-components: motivation to obtain rewards ("wanting"), consumption of rewards ("liking") and learning what predicts reward ("learning"; Berridge et al., 2009). These components broadly map onto the three different stages of pleasure: appetitive, consummatory and remembering (Thomsen et al., 2015). Preclinical studies have shown that these sub-components can be dissociated behaviourally, and that they have partially dissociable neural systems (Berridge et al., 2009). Importantly, it has been proposed that in humans these components have both a conscious component (which may be assessed using self-report measures) and an unconscious component (which may only be accessible using objective measures; Berridge et al., 2009; Thomsen et al., 2015).

The first evidence for a dissociation between reward components came from preclinical studies by Berridge and Robinson (Berridge & Robinson, 1998). In their seminal rodent studies, they were able to demonstrate a dissociation between behavioural measures that assess "wanting" (measured as choice preference, consumption or operant effortful responses for food) and "liking" (measured as orofacial reactions to sucrose such as tongue protrusions; Berridge & Robinson, 1998). Using these different behavioural tasks, they demonstrated that whilst dopamine depletion did not alter "liking" of sucrose, it did reduce "wanting" of sucrose (Berridge et al., 1989), suggesting that dopamine plays a critical role in "wanting" but not "liking". Subsequent work from lesion and electrode stimulation studies demonstrated that the neural systems mediating "wanting" are neurochemically and anatomically diverse, whereas "liking" is generated by "hedonic hotspots" which are anatomically small (e.g., embedded in the ventral pallidum, nucleus accumbens, orbitofrontal cortex and insula) and neurochemically constrained (opioids, endocannabinoids and GABA-benzodiazepines; see

Berridge & Kringelbach, 2015; Morales & Berridge, 2020 for reviews). Thus, whilst "wanting" depends heavily on dopamine, "liking" is more reliably linked to opioid and endocannabinoid pathways (Dillon et al., 2014). This distinction has also been extended to distinguish "reward learning", which is dissociable from "wanting" (see Berridge et al., 2009).

Since then, researchers have further fractionated reward processing into smaller components (Husain & Roiser, 2018). For example, theoretically it has been divided into many sub-components, including but not limited to: anticipation, decision-making, motivation, sensitivity, learning and memory. The precise components are debated and unfortunately there has been a lack of consistent terminology within the literature (e.g., Husain & Roiser, 2018; Rizvi et al., 2016; Rzepa et al., 2017; Treadway & Zald, 2013). Nevertheless, research that attempts to dissociate different components of reward processing will help to refine this construct and subsequently aid terminology. Similar to preclinical work and research in other fields (such as memory), this effort will require studies to demonstrate dissociations between components (e.g., using a battery of behavioural tasks).

1.4.4. Reward processing deficits in anhedonia

Increasing evidence suggests that anhedonia is related to aberrant reward processing (Pizzagalli et al., 2005; Treadway et al., 2009). However, as discussed above, reward processing is not a unitary construct (Berridge & Robinson, 2003). Given the fractionation of reward processing, a pivotal question that arises is precisely what aspects of reward processing are altered in people with anhedonia. As these different components are suggested to differ neurochemically and neuroanatomically (Berridge et al., 2009), this could have important implications for treatment. For example, a patient with dysfunctional reward motivation may respond better to a dopaminergic drug than a patient with a deficit in the experience of reward (Thomsen, 2015; Treadway & Zald, 2011). To address this question, there is a need for behavioural measures in humans that dissociate different sub-components. Given the wealth and success of preclinical research

dissociating reward components (Berridge et al., 2009), translating behavioural tasks from animals to humans may be a promising approach.

1.4.5. Translational research

Animal models are a key tool for investigating the biological mechanisms which underpin anhedonia (via direct brain manipulations to enable causal inference)(Robinson, 2016; Treadway & Zald, 2013). They are also used in the discovery and development of novel pharmacological treatments (Robinson, 2016). Unfortunately, despite a large investment from pharmaceutical companies, antidepressants that appear promising in preclinical trials have frequently failed to demonstrate efficacy in clinical trials (Belzung, 2014; Garner, 2014). There are many possible reasons for this unsuccessful drug development (Belzung, 2014; Garner, 2014). However, one important factor which has been proposed is the discrepancy in how depression and its symptoms are measured in preclinical and clinical research (Aylward et al., 2019; Badre et al., 2015; Garner, 2014). Whilst clinical studies rely on self-report measures, preclinical studies rely on behavioural outcomes. At present, most behavioural measures used in preclinical depression trials (forced swim test, tail suspension test) cannot be applied in humans (Porsolt et al., 1977; Steru et al., 1985). However, studies have started to use behavioural measures that can be applied in both human and rodent research (Aylward et al., 2019; Pizzagalli et al., 2005; Treadway et al., 2009).

This is particularly the case in the field of reward processing, with tasks being designed that attempt to tap into different domains of reward-related behaviour (Young & Markou, 2015). Examples of some promising translational paradigms are included in Table 1.4. It is important to note that there are several components of reward processing that do not yet have translational assays such as reward *anticipation and memory* (Robinson, 2018; Slaney et al., 2018; see Table 1.4). It is also worth highlighting that some of these assays, such as the Judgement Bias Task (Hales et al., 2016), have only very recently been developed into human versions (Aylward et al., 2019; Daniel-Watanabe et al., 2020) but have

already demonstrated promising cross-species findings in relation to depression (Aylward et al., 2019; Hales et al., 2014). Overall, this field is still in its primacy and demonstrating translational validity of these assays is a challenging and evolving process. Nevertheless, the development of objective measures that can be used in both human and rodent research opens up an exciting research avenue that may help bridge the gap between clinical and preclinical research (Aylward et al., 2019; Der-Avakian & Pizzagalli, 2018; Pike et al., 2021).

Table 1.4. Translational reward processing tasks and gaps in the literature (modified from Slaney et al., 2018)

Reward component	Human Task	Rodent Task
Motivation	Progressive Ratio EEfRT	Progressive Ratio Effort-based choice tasks
Sensitivity	Sweet Taste Test	Sucrose Preference Test
Learning	Probabilistic (RBPRT, PSST, PRLT) Pavlovian conditioning	Probabilistic (RBPRT, PSST, PRLT) Pavlovian conditioning
Anticipation	N/A	Successive contrast tasks
Memory	N/A	Reward Learning Assay Affective Bias Test
Decision-making	EEfRT Judgement bias task	Effort-based choice task Judgement bias task

Abbreviations: EEfRT, Effort-Expenditure for Rewards Task; RBPRT, Response Bias Probabilistic Reward Task; PSST, Probabilistic Stimulus Selection Task; PRLT, Probabilistic Reversal Learning Task.

Relevant to this thesis, I will now discuss the behavioural evidence for reward processing deficits in people with anhedonia using translational tasks, focussing on the three main components of reward: reward motivation, reward sensitivity and reward learning. To ensure clarity, I have provided a definition of each component in Table 1.5. Due to the limited number of studies that measure anhedonia and its severity (using

anhedonia questionnaires; Thomsen et al., 2015), I will include evidence from clinical disorders in which anhedonia is prevalent, focusing on depression. It is important to note that this is not an exhaustive review. Instead, I will discuss *human tasks* that have, or have the potential to be, translated across species (see Halahakoon et al., 2020 and Thomsen, 2015 for reviews). I will then discuss gaps in the current literature, before outlining the aims of this thesis.

Table 1.5. Glossary

Reward component	Definition
Reward motivation	"Incentive or desire to act, or accomplish goals"
Reward sensitivity	Consummatory experience of reward
Reward learning	Ability to learn and remember stimulus-response and action-response associations in an attempt to maximise future rewards

1.4.5.1. Reward motivation

Reward motivation can be defined as the "incentive or desire to act or accomplish goals" (Der-Avakian et al., 2016). In behavioural studies, this is often operationalised as willingness to exert effort for reward (Chong et al., 2016). Based on preclinical rodent tasks, human reward motivation tasks have recently been developed that measure (1) effort-related choice (i.e., decision-making) or (2) effort-expended for reward (Hodos, 1961; Salamone et al., 2018). In humans, the three most commonly used behavioural tasks are the Effort Expenditure for Reward Task (EEfRT; Treadway et al., 2009), the Progressive Ratio Task (PRT; Strauss et al., 2016) and the Handgrip task (Cléry-Melin et al., 2011).

The most commonly used reward motivation task in humans is the EEfRT (Treadway et al., 2009). This is an effort-based decision-making task, based on a procedurally similar rodent task (Salamone et al., 2018). In the EEfRT, participants must choose between a high effort/high reward option (100 button presses within 21 seconds for $1.24 to $4.30) and a

low effort/low reward option (30 button presses within 7 seconds for $1; Treadway et al., 2009). Trials also contain a visible probability cue which indicates the probability of the trial being a "win" trial: 12%, 50%, 88%. Participants are informed that two "win" trials will be paid to them at the end of the task. In this task, motivation is operationalised as choice preference, with an increased bias towards the high-effort option indicating increased reward motivation. Initial validation of this task demonstrated that acute administration of amphetamine increased bias towards the high-effort option in both humans and rats, providing some translational validity (Bardgett et al., 2009; Soder et al., 2020; Wardle et al., 2011).

People with depression and schizophrenia also show a reduced bias towards the high-effort option compared to healthy controls (Tran et al., 2020; Treadway et al., 2012; Wang & Gorenstein, 2013). Specifically, they were less likely to use information provided about the reward (such as the magnitude and probability of receiving the reward) to inform their choices (Yang et al., 2014). Importantly, in healthy volunteers, self-reported trait anhedonia was associated with reduced choice for the high-effort option (Treadway et al., 2009). These data have been used to support the claim that anhedonia is related to impairments in reward motivation. Nevertheless, there are potential confounds of this task that should also be ruled out such as delay and probability discounting (Chong et al., 2016). This means that individuals may show a reduced preference for the high-effort option not because they are less willing to exert effort for it, but rather because it takes longer to complete or has a lower probability of success. Furthermore, this task requires complex decision-making, which may be less appropriate for psychiatric populations who may have impaired information processing (i.e., tapping into cognitive ability rather than reward motivation; Chong et al., 2016).

Another reward motivation task, based on the gold-standard task used to measure reward motivation in rodents, is the PRT (Hodos, 1961). In this task, participants must perform exponentially more operant responses (e.g., button presses) to obtain the same amount of reward over subsequent trials (Strauss et al., 2016). The amount of effort the

participant will exert for a reward (referred to as their "breakpoint") is used as a measure of their motivation. This breakpoint is interpreted as the point at which the participant no longer perceives a given reward to be "worth the effort". In healthy controls, people display a higher breakpoint for higher value rewards, providing initial validation for this task as a measure of reward motivation (Roane et al., 2001).

Previous studies have shown that people with depression and bipolar disorder have a decreased breakpoint for monetary rewards compared to healthy controls, suggesting impairments in reward motivation (Hershenberg et al., 2016). In people with schizophrenia, a lower breakpoint was also associated with higher levels of avolition and anhedonia on a negative symptom scale (Strauss et al., 2016). Despite studies in clinical populations showing reduced reward motivation on this task (Hershenberg et al., 2016), some animal models of depression which attempt to induce depressive-like states (maternal separation and chronic mild stress) have failed to find a similar reduction in breakpoint (Barr & Phillips, 1998; Shalev & Kafkafi, 2002; although see Olausson et al., 2013) questioning the translational validity of this task. It is important to note that unlike the rodent version, most of the human versions of this task require an additional explicit choice (accept or reject a trial) to be made prior to initiating the trial, which may contribute to the discrepancy observed across species. Moreover, the PRT fails to account for some important potential confounds such as delay intolerance and motor impairments. This means that a decreased breakpoint may not reflect a reduced willingness to exert effort for reward but rather intolerance to wait for reward or poorer motor ability; Chong et al., 2016).

Another task used to measure reward motivation is the handgrip task (Cléry-Melin et al., 2011; Schmidt et al., 2008). Unlike previous tasks, it does not have a procedurally similar rodent task. However, as it has a clear behavioural output and has the potential for translation, it is discussed here. In this task, participants are asked to squeeze on a handheld dynamometer in response to different reward magnitudes (1 cent, 10 cents or 1 euro). Participants are informed that the stake that they will obtain is proportional to the amount of effort exerted on a given

trial. Reward motivation is measured as an individual's physical force exerted on the handgrip. To my knowledge, no studies have examined anhedonia in relation to performance on this task and only one study has examined depression. Unlike healthy controls, people with depression did not exert more effort for the high compared to low reward trials (Cléry-Melin et al., 2011). This supports the claim that people with depression have reduced reward motivation. Unlike the EEfRT, this task is less complex and therefore may better account for potential confounds such as impaired information processing. However, this study included a hospitalised inpatient population with severe depression. Consequently, it is unclear whether this deficit is specifically related to the symptom of anhedonia or instead reflects other symptoms or a global dysfunction. It is important to note that the majority of studies that have continued to use this apparatus have adapted the task to measure decision-making (e.g., alternative choice, accept vs reject trials).

Although not based on rodent tasks, there are two other studies worth mentioning that have examined reward motivation and anhedonia. Sherdell et al. (2012) found that increased anticipatory anhedonia (items on a depression scale) predicted decreased motivation to view humorous cartoons on an effort-based choice task. Also, using a button pressing task in depressed adolescents, Rzepa & McCabe (2019) found that higher anticipatory anhedonia (TEPS – anticipatory scale) was associated with a decreased number of button presses to receive chocolate (although see Rzepa et al., 2017; Rzepa & McCabe, 2019). Given that there are important differences in reward processing in adolescence, it would be important to try to replicate this finding in adults (Galvan, 2010; Halahakoon et al., 2020). Together, these two findings support the theory that anhedonia is related to reduced motivation.

In summary, few studies to date have objectively measured reward motivation impairments in relation to anhedonia (Pessiglione et al., 2018). Instead, most studies have examined clinical diagnostic groups such as depression. Moreover, the majority of studies have focused on explicit choice (decision-making), leaving the evidence for deficits in

absolute physical effort-expenditure for reward sparse (see Halahakoon et al., 2020 for a recent review mentioning this).

1.4.5.2. Reward sensitivity

Reward sensitivity is defined as the consummatory experience of reward. Attempts to translate reward sensitivity tasks from rodents to humans have proven difficult (Thomsen, 2015). Nevertheless, some attempts have been made such as the sweet taste test.

The sweet taste test is based on the gold-standard measure of reward sensitivity in rodents, the Sucrose Preference Test (Willner et al., 1987). This task measures an animals ability to detect, and demonstrate a preference for, a weak sucrose solution over water (Willner et al., 1987). Although different variations have been used in humans, they typically require participants to report the intensity and pleasantness of different sucrose concentrations. The measurement of both intensity and pleasantness is in line with the rodent task, whereby a reduced sucrose preference could be due to either a decreased ability to detect sucrose (i.e., altered intensity) and/or decreased experience of pleasure from sucrose (i.e., altered pleasantness).

People with depression have often displayed similar pleasantness ratings of sucrose compared to healthy controls (Amsterdam et al., 1987; Berlin et al., 1998; Dichter et al., 2010). However, in one study in healthy volunteers, self-reported anhedonia was associated with reduced liking of a high concentration of sucrose (Bedwell et al., 2019). Taken together, it is unclear whether anhedonia is related to reduced liking on a sweet taste test. There has also been discrepancy between studies measuring sucrose intensity. Compared to healthy controls, some studies have reported poorer detection of sucrose in people with depression (Amsterdam et al., 1987; Berlin et al., 1998), whilst others have reported no clear difference between groups (Dichter et al., 2010). Similarly, Bedwell et al. (2019) reported that sucrose sensitivity did not correlate with anhedonia. There are several factors which could account for these conflicting findings. One potential explanation is that point scales, which are often used to

measure intensity and pleasantness, may not be sensitive enough to reliably detect impairments (McCabe, 2018).

Although not based on rodent tasks, it is of relevance to note that human paradigms used to measure hedonic capacity have also found conflicting findings in depressed participants (Allen et al., 1999; Berenbaum & Oltmanns, 1992; Dunn et al., 2004; Renneberg et al., 2005; Sloan et al., 2001; Treadway & Zald, 2011; Trémeau et al., 2005). These studies typically asked participants to rate their experience (pleasantness, emotional response or arousal) of positively valanced stimuli such as faces/films or examined physical responses (facial expressions, heart rate) to positively valanced stimuli. Additionally, McCabe and colleagues reported that adolescents with symptoms of depression (Rzepa et al., 2017) displayed blunted neural responses whilst tasting chocolate, despite not differing on self-report measures (liking and intensity of chocolate after tasting it). This is important as it could further support the possibility that point scales have inadequate sensitivity to detect differences (McCabe, 2018).

In summary, there is some evidence for reward sensitivity impairments in people with depression (Amsterdam et al., 1987; Berlin et al., 1998), although this finding is not always replicated (Dichter et al., 2010). One reason for this discrepancy may be their over-reliance on point scales and the failure to assess anhedonia and its severity. To date, there has been difficulty measuring reward sensitivity in humans using translational tasks.

1.4.5.3. Reward learning and memory

In this thesis, reward learning and memory refers to the ability to learn and remember stimulus-response and/or action-response associations in an attempt to maximise future rewards. Three translational reward learning tasks are the Response Bias Probabilistic Reward Task (RBPRT; Pizzagalli et al., 2005) the Probabilistic Stimulus Selection Task (PSST; Frank et al., 2004) and the Probabilistic Reversal Learning Task (Cools et al., 2002)

The Response Bias Probabilistic Reward Task (RBPRT) was developed to measure an individual's tendency to adjust their behaviour in order to maximize future reward (Pizzagalli et al., 2005). Unlike most of the tasks mentioned so far, this task was initially developed in humans and then translated to rodents (Der-Avakian et al., 2013; Kangas et al., 2020) and more recently marmosets (Wooldridge et al., 2020) using procedurally similar paradigms. In the human version, participants are asked to report the length (short or long) of an ambiguous, briefly presented, mouth (100 ms) on a schematic face. Unknown to the participant, there is an asymmetric reinforcement ratio (3:1): correctly choosing one mouth length ("rich stimulus") has a higher probability of reward feedback (3 times more) than correctly choosing the other mouth length ("lean stimulus") (Pizzagalli et al., 2005; Whitton, Reinen, et al., 2020). The outcome on this task is response bias (i.e., bias towards choosing the mouth most frequently associated with reward feedback, regardless of accuracy). Healthy volunteers developed a bias towards choosing the "rich" stimulus which was associated with a higher probability of reward (Pizzagalli et al., 2005). Pharmacological manipulations in human and rodent studies have demonstrated similar response biases (nicotine withdrawal resulted in reduced bias), providing some translational validity (Barr et al., 2008; Der-Avakian et al., 2013; Pergadia et al., 2014).

People with depression and bipolar disorder show a reduced response bias compared to healthy controls on the RBPRT (Pizzagalli et al., 2008; Vrieze et al., 2013), indicating reduced responsiveness to reward feedback in these patients. Moreover, the reduced bias in depressed patients persists following the remission of symptoms (Petchell, 2013), suggesting it could be an underlying endophenotype. Importantly, the reduced bias in depressed patients was particularly pronounced in those with higher trait anhedonia, which may suggest that this deficit is particularly related to anhedonia (Pizzagalli et al., 2008). Whilst this task is promising, it is difficult to discern whether a reduced bias on the task reflects impairments in reward learning and/or hedonic response (Huys et al., 2013). This means that a participant may not show a bias because they

cannot learn about the cue-reward association, or because they are not sensitive to the reward feedback.

Another task which measures reward learning is the PSST (Frank et al., 2004), which also has a similar rodent version (Trecker et al., 2012). In the human task, participants must choose between one of two letters presented in pairs (A+B, C+D, E+F). In each pair, one of the letters has a higher probability of receiving a correct response. For example, the probability ratios are: A+B (80:20), C+D (70:30), E+F (60:40). Therefore, participants should learn to choose the letters A, C and E more often than B, D and F. In the test phase, participants are presented with novel combinations of pairs, all of which include the letter A (high probability of reward) or B (high probability of no reward). In the test phase, no feedback is provided. Reward learning is operationalised as bias towards the letter A (punishment learning is also measured as bias away from B). Healthy volunteers have demonstrated learning from reward and punishment on this task (Frank et al., 2004). People with depression, Parkinson's disease and schizophrenia show impairments in reward learning on this task, when compared to healthy controls (Chase et al., 2010; Frank et al., 2004; Waltz et al., 2007). However, it is important to consider the limitations of this task. One important limitation of this task is its complexity. For example, follow-up studies have failed to show adequate learning during training on this task and have failed to replicate the finding in Parkinson's disease (Grogan et al., 2017).

The Probabilistic Reversal Learning Task (Cools et al., 2002) also measures learning and sensitivity to positive and negative feedback. The rodent version of this task is procedurally similar (Bari et al., 2010). In the human version, participants are presented with a pair of abstract stimuli that have different reward contingencies. For example, one stimulus has a high probability of positive feedback (80% green smiley face) and a low probability of negative feedback (20% red sad face), whereas the other stimulus has the opposite contingencies (80% negative, 20% positive). Therefore, participants must learn which stimulus is associated with a higher probability of positive feedback. Interestingly, during the task the stimulus-feedback contingencies

reverse, which means that the image that was previously associated with a higher probability of positive feedback is now associated with a higher probability of negative feedback (and vice versa). Outcomes of interest include reversal learning and sensitivity to positive ("win-stay") and negative feedback ("lose-shift"). People with depression show impairments on this task, although the precise deficits (reversal learning, hyposensitivity to reward, hypersensitivity to punishment) varies across studies (Dombrovski et al., 2010; Mukherjee et al., 2020; Murphy et al., 2003; Robinson et al., 2012; Tavares et al., 2008), although see (Brolsma et al., 2020).

In summary, there is some evidence that people with depression show impairments in reward learning. The evidence for reward learning deficits being specific to the symptom of anhedonia is sparse. To date, these tasks have all focused on learning within a single test session (i.e., over a short period of time: ~ 20 minutes; Wimmer et al., 2018). There are few behavioural tasks available that measure reward learning *and memory* over multiple days. This is a missing gap in the literature: in animal studies and in our everyday life we often learn and consolidate information over longer time periods (Wimmer et al., 2018).

1.5. Gaps in the Literature

Despite progress in the field of anhedonia and reward processing, there are several gaps in the current literature that need to be addressed.

First, there are few reward processing tasks that measure specific sub-components of reward in humans (motivation, sensitivity or learning; Keren et al., 2018; Thomsen, 2015). If we are to gain a clearer understanding of the taxonomy of reward processing and its dysfunction in anhedonia, we need to have behavioural tasks that assess different components (Husain & Roiser, 2018).

Second, most studies investigating anhedonia compare people with depression to healthy controls (McCabe, 2018). This is surprising, as only 37% people with depression exhibit significant levels of anhedonia (Pelizza & Ferrari, 2009). Thus, comparing people with depression to healthy controls to investigate anhedonia could mask important findings.

There is a need for studies to directly measure anhedonia and its severity using anhedonia questionnaires (Der-Avakian & Markou, 2012; McCabe, 2018). This may help to address whether reward dysfunctions are specific to anhedonia or related to other symptoms of depression (Nielson et al., 2020).

Finally, few studies have assessed several reward components using a battery of tasks in the same sample. Instead, most studies have examined anhedonia and reward processing using a single anhedonia questionnaire and/or single task, respectively. This may have led to incomplete conclusions (Nielson et al., 2020). For example, it is unclear whether anhedonia reflects a generalised reward deficit (individuals with poorer reward sensitivity also have poorer reward motivation) or specific deficits (there are sub-groups of anhedonia patients with different impairments). Employing a battery of tasks (ideally tasks with rodent analogues to facilitate translation) and self-report measures will enable us to investigate dissociations between reward processes and therefore provide a more holistic understanding of anhedonia (Husain & Roiser, 2018; Nielson et al., 2020). In the following, I will describe the aims of this thesis, and link them to the gaps in the literature.

1.6. Aims of this thesis

Chapter 2: Provide proof-of-concept for a novel reward motivation task which measures physical effort-expenditure for reward in a non-clinical population.

The most commonly used human reward motivation tasks measure effort-based decision-making (i.e., choice), predominantly using the EEfRT. As this may be distinct from effort-expenditure for reward (i.e., action; Lockwood et al., 2017), there is a need for behavioural tasks that measure this aspect of reward motivation in humans (Halahakoon et al., 2020; Strauss et al., 2016). This is necessary for future studies aiming to delineate the precise motivational deficits related to anhedonia.

Chapter 3: Examine different components of reward processing (reward sensitivity and reward motivation) using a battery of

behavioural tasks in a non-clinical population with high versus low anhedonia.

To date, most studies have examined only one sub-component of reward (e.g., motivation) using a single task. Using a battery of behavioural tasks designed to probe different reward components (e.g., motivation, sensitivity) is necessary to demonstrate that these sub-domains can be dissociated in people, and to understand whether anhedonia is related to a general reward deficit or specific to certain reward components (Husain & Roiser, 2018; Nielson et al., 2020). Whilst anhedonia is a clinical symptom, it can be observed to varying degrees in the typical population (Franken et al., 2007). The advantage of examining anhedonia in non-clinical populations is that they are less likely to experience comorbidity, take psychiatric medications and experience cognitive deficits; all of which can confound the interpretation of clinical data (Harvey et al., 2007).

Chapter 4: Develop a translational reward learning and memory task in humans based on a procedurally similar rodent task.

To date, few translational tasks are available that assess distinct components of reward -- especially in relation to reward memory. Here, I focus on developing a novel computerised human task based on a rodent task: the reward learning assay (RLA; Robinson, 2018), which has shown important deficits in putative rodent models of depression (Robinson, 2018; Stuart et al., 2019). Unlike most of the human tasks available in the literature (Wimmer et al., 2018), this task measures reward learning and memory over 5 days, analogous to the rodent task.

Chapter 5: Examine the three main components of reward processing (reward sensitivity, reward motivation and reward learning and memory) using a battery of tasks in the same population of people who meet criteria for depression.

This study was designed to address the three main components of reward processing in people experiencing depression using a battery of translational behavioural tasks and anhedonia questionnaires. Whilst the primary analysis aimed to compare people who experienced depression

versus healthy controls, secondary analyses were planned to examine whether anhedonia could be a moderating or mediating factor. This extends the findings from Chapter 3, by examining a population with clinical levels of anhedonia. Due to COVID-19, this study had to be stopped and data collection to the pre-registered sample size was not possible. However, here I present the data collected so far as a preliminary data set.

Thus, in relation to the gaps in the literature stated above, Chapter 2 and Chapter 4 contribute to the first gap in the literature (*lack of behavioural tasks measuring distinct components of reward*) by developing a reward motivation task (Chapter 2) and a reward learning and memory task (Chapter 4) in humans. Chapter 3 and Chapter 5 address the second (*lack of studies directly assessing anhedonia and its severity using anhedonia questionnaires*) and third gaps (*lack of studies employing a battery of tasks and self-report measures in the same population*) in the literature by employing a battery of behavioural tasks and anhedonia measures in the same population of people with either higher levels of anhedonia in a non-clinical population (Chapter 3) or a depressed population (Chapter 5).

Chapter 2: Joystick-Operated Reward Runway Task (proof-of-concept)

Chapter Aim: Provide proof-of-concept for a novel reward motivation task that measures physical effort expenditure for reward: the Joystick-Operated Reward Runway Task (JORT).

Acknowledgments: Dr Robert Davis for programming the JORT and Dr Adam Perkins for providing feedback on the task design.

2.1. Introduction

Self-reported deficits in motivation are common in many psychiatric and neurological disorders and are associated with a diminished quality of life (Benito-León et al., 2012; Husain & Roiser, 2018). Currently available treatments fail to effectively address this debilitating symptom (Strauss et al., 2014). In line with the RDoC, there is a need for behavioural paradigms that objectively measure motivation in humans (Horan et al., 2015; Treadway et al., 2009). This may provide a better understanding of the *precise* mechanisms underlying self-reported symptoms (e.g., symptoms of apathy, anergia, fatigue), allow us to dissociate reward motivation deficits from other reward deficits and enable us to more appropriately target treatments (Halahakoon et al., 2020; Husain & Roiser, 2018).

2.1.1. Subjective measures of motivation

In clinical practice, motivation is typically assessed using self-report questionnaires and clinical interviews (Husain & Roiser, 2018). This includes scales such as the BIS/BAS (Carver & White, 1994), Lille Apathy Rating Scale (Sockeel et al., 2006), Apathy Evaluation Scale (AES; Marin et al., 1991) and the Apathy Scale (Starkstein et al., 1992). Clinically, these scales are useful as they help clinicians to identify that a patient is experiencing problems in motivation (Pessiglione et al., 2018). However, as mentioned in section 1.3.5, there are limitations of over-relying on questionnaires. First, they require patient insight which may be compromised in some patients (Pessiglione et al., 2018). Secondly, they are usually validated in either patient populations or healthy controls, not both (Chong et al., 2016; Weiser & Garibaldi, 2015). Thirdly, they do not provide a mechanistic understanding of the underlying deficit (Husain & Roiser, 2018). Finally, they may lack the sensitivity to detect slight motivational impairments (Chong et al., 2016). To address these limitations, one approach is to employ objective measures of motivation alongside subjective scales (Horan et al., 2015; Pessiglione et al., 2018).

2.1.2. Objective measures of motivation

There is a vast preclinical animal literature examining motivation using objective behavioural tasks (Halahakoon et al., 2020; Salamone et al., 2018). In these studies, motivation is operationalised as the willingness to overcome costs (usually physical effort) to obtain a reward (food pellets; Chong et al., 2016). These behavioural tasks can broadly be divided into those that measure effort-based choice (Salamone et al., 1994), or more commonly, by measuring the amount of physical effort exerted for a reward (e.g., progressive ratio task; Hodos, 1961; Pessiglione et al., 2018), see Figure 2.1.

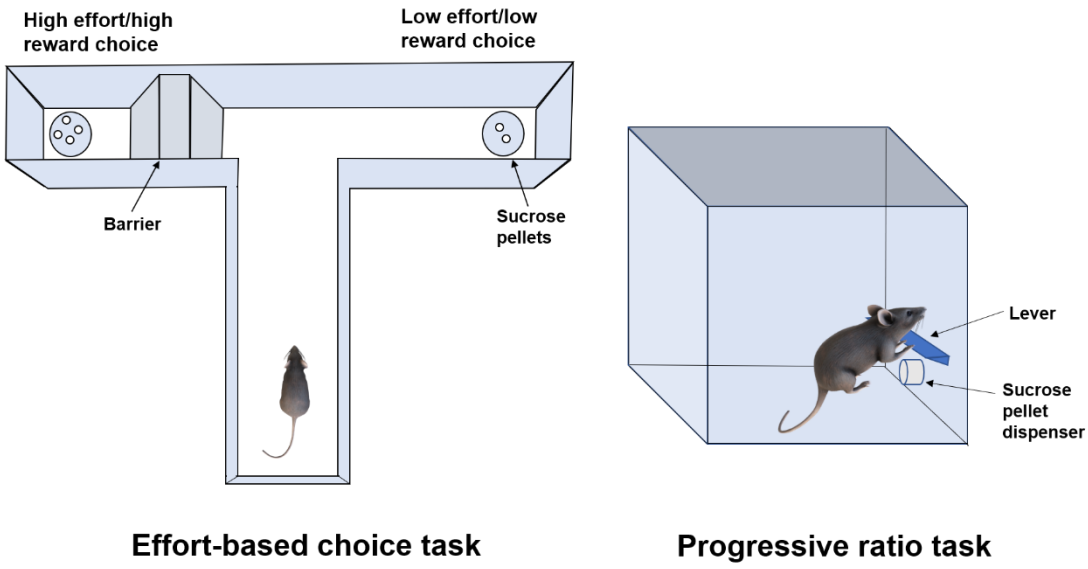

Figure 2.1 Reward motivation tasks commonly used in rodents: effort-based choice task and progressive ratio (amount of effort exerted for reward)

Recently, there have been attempts to develop similar behavioural tasks in humans (as discussed in section 1.4.5.1; see Chong et al., 2016; Pessiglione et al., 2018 for reviews). However, there are gaps in the current human literature: (1) there are very few standardised motivation tasks, as highlighted in the RDoC (NIMH, 2016) and (2) most tasks have focused on measuring effort-based choice (i.e. decision-making; EEfRT), with few tasks measuring physical effort exerted for reward (Chong et al., 2016; Halahakoon et al., 2020; Pessiglione et al., 2018). Whilst effort-

based decision-making tasks have provided useful insights into choice behaviour (Treadway et al., 2009), it is important to also develop tasks based purely on physical effort for reward as it is often the only dependent outcome in many preclinical operant reward motivation tasks (Beierholm et al., 2013) and it is less likely to be confounded by cognitive ability or cognitive effort (see Cooper et al., 2018).

2.1.3. Study Aim

To address this gap, the aim of this study was to provide proof-of-concept for a novel reward motivation task: the Joystick-Operated Reward Runway Task (JORT). The JORT was originally developed as an objective measure of fear and anxiety based on a rodent runway task (see Perkins et al., 2009). Here, we modified the JORT to measure a person's physical effort-expenditure for reward. In this task, participants must push on a force-sensing joystick (PS-JS1, Psyal, London, UK) to chase and catch an onscreen target. Trials vary in the amount of reward on offer (points: 0, 10, 100, 1,000) and effort required to win (50, 80, 100, 120% of a person's maximum calibrated force). Additionally, participants completed self-report measures to assess motivation (BIS/BAS; Carver & White, 1994), depression symptoms (Beck Depression Inventory-II; Beck et al., 1996) and anhedonia symptoms (Chapman Physical Anhedonia Scale Revised; Chapman et al., 1976). Based on previous literature (see section 1.4.5.1), we predicted that participants will exert more physical force for higher, compared to lower, reward trials.

2.2. Method

2.2.1. Participants

Twenty-five participants took part in this study. Eligibility criteria were aged ≥ 18 years, fluent in English, good mental, and physical health with no current or previous diagnosis of a psychiatric illness (self-reported).

Participants were recruited via internal posters within the University of Bristol. All participants were reimbursed £10 for their time and were informed that they could win an additional performance-based pay (up to £5).

Ethics approval was obtained from the Faculty of Biomedical Sciences Research Ethics Committee at the University of Bristol. All participants provided written informed consent.

For this proof-of-concept study, a target sample size of 20 participants was chosen based on our previous experience with this type of task and a power calculation (G*Power 3.1; Faul et al., 2007) indicating that 19 participants provided sufficient power (.8) to detect a medium-to-large effect size (Cohen's *f* = 0.28; ANOVA: Repeated measures, within factors). However, due to some participants meeting an *a priori* exclusion criteria for this study (achieving trials designed to be impossible; see section 2.3.2), the sample size was increased to 25 participants during recruitment to account for this (prior to data analysis). Given that the purpose of developing this task was for later use in a clinical study, we were interested in detecting a medium-to-large effect size in a non-clinical population to ensure a reasonable comparison baseline to which the clinical populations would be compared. Target sample size was 20 participants; achieved sample size for the primary outcome (average force) was 18 participants.

2.2.2. Joystick-Operated Reward Runway Task (JORT)

The JORT measures a person's willingness to exert physical effort to achieve a goal (Perkins et al., 2009; PH-JS1, Psyal, London). On each trial in this reward version, there is a cursor (representing the participant) located along a runway and a cue in the top left-hand corner of the screen which indicates the number of points on offer: 0, 10, 100 or 1,000 points, see Figure 2.2. There is also a cue indicating the cumulative total number of points won in the top right-hand corner of the screen. This is followed by the presentation of a target (black dot), located ahead of the participant, which accelerates away from the participant along a straight forward trajectory (i.e., the runway) until it leaves the screen (if not caught up with). To win the points on offer, the participant is required to push the joystick to chase and catch up with the target. The force applied on the joystick determines the speed at which the participants cursor moves along the runway (Perkins et al., 2009). Trials vary in the number

of points on offer (0, 10, 100 and 1,000 points; visible to the participant) and the minimum effort required to win (50, 80, 100 or 120% of their maximum calibrated force; not visible to the participant). If the participant catches the target, they receive feedback that they have won the number of points on offer. If they fail to catch the target, they do not receive any feedback. Trials end either upon catching the target or after 7 seconds. The inter-trial interval varies pseudo-randomly between 3 and 7 seconds. After each trial, the next trial automatically starts. Force applied is recorded approximately every 15 ms.

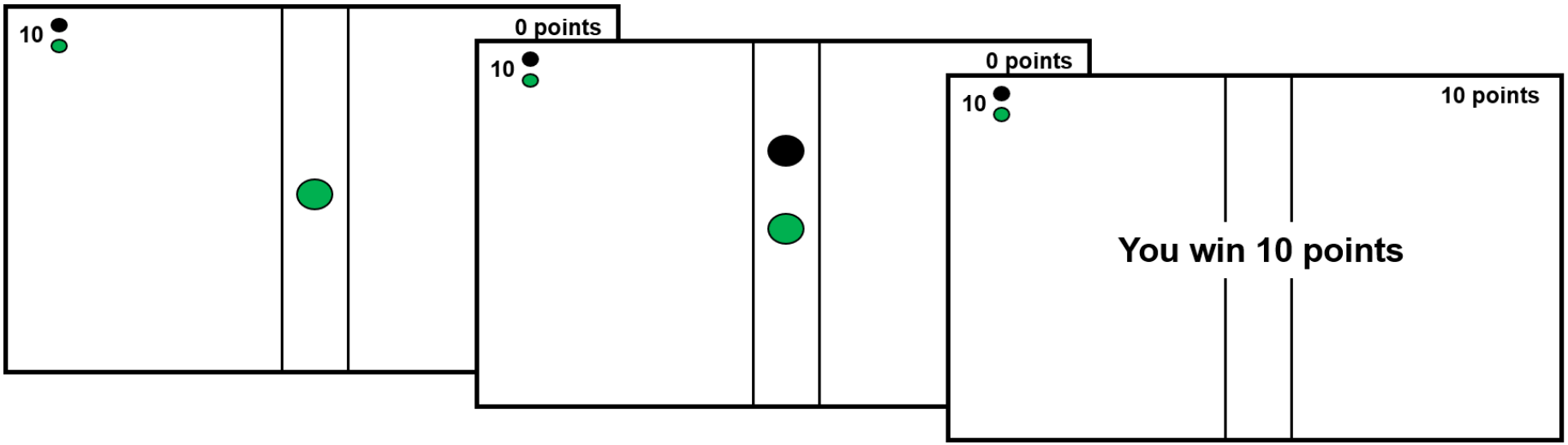

Figure 2.2 An example trial on the Joystick-Operated Reward Runway Task (JORT) The green dot (representing the participant) is initially displayed with a cue indicating the number of points on offer. This is followed by the presentation of the target (a black dot). The participant then receives feedback if they catch the target (e.g., "You win 10 points") or no feedback if they fail to catch the target.

Participants completed 2 blocks of 48 trials (96 total). Each block consisted of an equal number of reward-effort combinations (*N* = 3), except for one combination where only 2 trials were presented due to experimenter error (0 points - 80% effort in second block). There was a short break in between each block. All participants completed the same pre-randomised order of trials. The order of the trials was fixed across participants for practical reasons. The task is currently programmed using a script which indicates the start time, end time and effort required on each trial individually. Using this current version, running the task without a fixed order of trials would require creating multiple scripts for each participant.

Prior to the task, participants were given standardised verbal instructions, completed a calibration phase followed by four practice trials. In the calibration phase, participants are asked to push the joystick as hard as they can five times whenever the word "GO" is presented on the screen (Perkins et al., 2009). The apparatus measures 0 – 500 newtons of force exerted on the joystick (Perkins et al., 2009). A participant's maximum calibrated force is determined by their peak force reached during the calibration phase. This is used to standardise the amount of effort required across participants. In the practice trials, participants encounter each reward and effort level to familiarise themselves with the task. Participants were informed that the total number of points won during one of the two blocks (chosen randomly) directly corresponded to the amount of money they would win (i.e., performance-based pay of up to £5).

Payment is based on performance on the task. Specifically, it was calculated as the number of points won on a block (chosen at random) multiplied by 0.0005005 (rounded to the nearest integer). This divided the maximum reward on offer (£5) by the maximum number of obtainable points (9990 points) such that the amount won was proportional to performance. If participants achieved over 9990 points, they received the full reimbursement of £5.

The task is programmed in C++ by Psyal (http://www.psyal.com/) and includes modifiable parameters. In this version, the following parameters were used: acceleration of the target dot (pixels per frame) is 0.03 and maximum speed (pixels per frame) is 10. These parameters were chosen following piloting to ensure that the 50% effort trials were always obtainable, and the 120% effort trials were not obtainable. Effort trials refer to the minimum amount of effort required to catch up with the target dot. For example, 50% effort scales the target dot to 50% of the participants maximum force and therefore their velocity in the task.

The primary outcome of interest was relative average force. Secondary outcome variables were maximum force and reaction time. For relative average force and maximum force, mean force was divided by a participant's personal maximum force to standardise performance. Trials where no force was exerted were included as 0 in the average force and maximum force; and were excluded from the mean reaction time calculations. Reaction time on a given trial is the difference between the time at which force was exerted (> 2 N) and stimulus onset (when the target appeared).

2.2.3. Self-report questionnaires

Behavioural Inhibition System and Behavioural Activation System Scales (BIS/BAS)

The BIS/BAS (Carver & White, 1994) was used to measure the two motivational systems: motivation to avoid aversive outcomes and motivation to pursue appetitive outcomes, respectively (Carver & White, 1994). This questionnaire asks participants to report whether they agree or disagree with statements using a 4-point scale which ranges from 1 (very true for me) to 4 (very false for me). The scale has four subscales. One subscale measures the BIS (7-items). The other subscales measure different aspects of the BAS: reward responsiveness, drive, and fun seeking. A higher score indicates higher BIS or BAS, respectively.

Depression (Beck Depression Inventory; BDI-II)

The BDI-II was used to measure symptoms of depression (Beck et al., 1996). This questionnaire asks participants to report symptoms they have experienced over the last 2 weeks (Beck et al., 1996). Specifically, it contains 21 questions which are answered on a 4-point scale which ranges from 0 (no symptom present) to 3 (severe symptom). Total scores range from 0 to 63 (higher scores indicate increased severity of depression). The BDI-II has good convergent validity with the revised Hamilton Rating Scale for Depression (r = .66 to .75), high internal consistency (a = ~ 0.9) and good test-retest reliability (range: .73 to .96; see Wang & Gorenstein, 2013). Due to experimenter error, one response option to the "changes in appetite" question was not available "3a. I have no appetite at all".

Anhedonia (Chapman Physical Anhedonia Scale; CPAS)

The CPAS (Chapman et al., 1976) was used to measure trait anhedonia. This questionnaire contains 61 statements which are rated on a 2-point true-false scale. Total scores range from 0 to 61 (higher scores indicate higher anhedonia symptoms). It was originally developed to measure anhedonia in Schizophrenia and has demonstrated good test-retest reliability (r = .74 to .86; Blanchard et al., 1998) and has some convergent validity with the SHAPS (Treadway et al., 2009).

2.2.4. Procedure

All participants were given the information sheet and provided informed written consent before completing the JORT. In between the two blocks on the JORT, participants completed the self-report questionnaires: CPAS, (Chapman et al., 1976), BDI-II (Beck et al., 1996) and the BIS/BAS (Carver & White, 1994). The experimenter remained out of sight and did not speak during testing, unless the participant required clarification on the task. All participants were tested individually. Upon completion of the study, participants were verbally debriefed and final consent was obtained.

2.2.5. Data Analysis

Python 3.6 and prism 8 were used to extract and visualise the data, respectively. Analyses were performed in SPSS 24 (IBM). Tests of ANOVA assumptions included checking for sphericity (Mauchly's Test), normality of the residuals (Kolmogorov-Smirnov and histograms) and potential outliers (scores 3 times greater than the interquartile range in any trial type, examined via boxplots). Greenhouse-Geiser statistics corrections were applied where Mauchly's Test of Sphericity was $p < .05$. Sensitivity analysis with any statistical outliers removed was conducted. All post-hoc comparisons were Bonferroni corrected for multiple comparisons. As this study was explorative at this stage (proof-of-concept), inferential statistics should be interpreted cautiously.

Primary analyses. Three dependent variables were considered: relative average force, maximum force, and reaction time. For each, a 2 x 4 x 4 (block x effort x reward) ANOVA was conducted. The within-subject's factors were block (2 levels: first or second), effort (4 levels: 50%, 80%, 100%, 120% of a participant's maximum calibrated force) and reward (4 levels: 0, 10, 100 or 1,000 points). Potential co-variates (main effects of age and sex) were checked.

Exclusion Criteria. Based on *a priori* criterion, participants who succeeded in over 75% trials were excluded from the analysis. This criterion was chosen as these participants must have achieved the 120% effort trials (designed to be impossible) and were therefore deemed to have not successfully reached their maximum force during the calibration phase. This was considered to be important as a previous pilot study ($N = 20$) revealed that when the task was too easy (required 50% effort), participants did not exert more force for higher reward trials, a finding which is in line with the law of least effort (i.e., people exert the least amount of effort required).

Exploratory analyses. Spearman's correlations were calculated to examine the association between performance on the JORT and self-report measures (BIS/BAS, BDI-II and CPAS).

2.3. Results

2.3.1. Participant characteristics

Twenty-five participants aged 18-39 years (12 female, mean age: 23.2 and *SD*: 5.3) took part in the study.

2.3.2. Exclusion criteria

Based on *a priori* criteria, seven participants succeeded in over 75% trials and were excluded from the analysis (N = 7). Achieving > 75% trials suggests that these participants achieved trials designed to be impossible (120% effort) and therefore did not achieve their maximum force during the calibration trials. A total of 18 participants were included in the analysis for relative average force and maximum force (mean age = 21.89, *SD* = 4.04, 7 females). For reaction time, a total of 16 participants were included in the analysis (N = 2 had missing data due to no response on 0-point trials).

2.3.3. Data Assumptions

Residuals for some trial types were not normally distributed based on Kolmogorov-Smirnov (maximum 5/32), thus caution must be taken in interpretation. Nevertheless, ANOVA is relatively robust to slight violations to the assumption of normality (Field, 2005). Statistical outliers were identified: relative average force (N = 3), relative maximum force (N = 1) and reaction time (N = 0). Removal of the outliers did not affect the findings, and therefore data will be presented with these participants retained in the analysis.

2.3.4. Joystick-Operated Reward Runway Task

Relative Average Force. There was strong evidence of a main effect of reward, $F_{(1.10,18.76)} = 8.91$, $p = .006$, $n_p^2 = .34$, see Figure 2.3. Participants exerted more force for higher reward magnitudes: 0 (M = 56.20, *SE* = 3.94), 10 (M = 63.36, *SE* = 1.58), 100 (M = 65.70, *SE* = 1.44) and 1000 (M = 69.21, *SE* = 1.61) points. Polynomial contrasts revealed evidence that this effect was linear (p = .005). Bonferroni-corrected pairwise comparisons revealed evidence of differences between all reward

magnitudes (*p*s ≤ .032), except between 0 points and 10 points (*p* = .172) and with weaker evidence of a difference between 0 and 100 points (*p* = .079). There was weak evidence of a main effect of block, $F_{(1,17)}$ = 4.60, *p* = .047, n_p^2 =.21. Participants exerted more force in the first block (*M* = 65.19, *SE* = 1.68) compared to the second block (*M* = 62.05, *SE* = 2.12). There was strong evidence of a main effect of effort, $F_{(1.62,27.59)}$ = 34.65, *p* < .001, n_p^2 = .67. Participants exerted more force for higher effort trials: 50% (*M* = 56.11, *SE* = 1.47), 80% (*M* = 65.30, *SE* = 1.29), 100% (*M* = 67.68, *SE* = 2.21) and 120% (*M* = 65.38, *SE* = 2.47). Bonferroni-corrected pairwise comparisons revealed participants exerted less force on the 50% effort trials compared to all other effort trials (*p*s < .001) and less force on 120% effort trials compared to 100% effort trials (*p* = .043). There was no evidence of a difference between 80% and 100% effort trials (*p*s ≥ .37). There was weak evidence of a block x reward interaction, $F_{(1.85,31.5)}$ = 3.35, *p* = .051, n_p^2 = .17. Bonferroni-corrected simple effects analysis revealed participants exerted less force in the second block compared to the first block on 0-point trials (*p* = .037), with weaker evidence of a difference between other reward magnitudes (*p*s ≥ .054). There was weak evidence of an effort x reward interaction, $F_{(3.06,51.95)}$ = 2.87, *p* = .044, n_p^2 = .15, with the effect of reward being largest on 120% effort trials. There was no evidence of other interactions (*p*s ≥ .46). Re-running the analysis with 3 statistical outliers excluded weakened the evidence for the main effect of block (*p* = .24). Re-running the analysis with age and sex as potential covariates revealed weak evidence of a main effect of sex (*p* = .092): males exerted a higher relative force (*M* = 66, *SE* = 2) than females (*M* = 60, *SE* = 3).

Re-running the analysis with all participants included (*N* = 25) weakened the evidence for the main effect of block (*p* = .15) and effort x reward interaction (*p* = .75) but improved the block x reward interaction (*p* = .007).

Relative Maximum Force. There was strong evidence of a main effect of reward, $F_{(1.11,\ 18.86)}$ = 9.26, *p* = .006, n_p^2 = .35, see Figure 2.3. Participants exerted a higher maximum force for higher reward magnitudes: 0 (*M* = 79.30, *SE* = 5.37), 10 (*M* = 91.08, *SE* = 2.53), 100

(*M* = 94.32, *SE* = 2.56) and 1000 (*M* = 98.73, *SE* = 2.94) points. Polynomial contrasts revealed evidence that this effect was linear (*p* = .004). Bonferroni corrected pairwise comparisons revealed evidence of a difference in maximum force exerted between 0 and 1000 points (*p* = .030), 10 and 100 points (*p* = .011) and 10 and 1000 points (*p* = .006). There was also weak evidence of a difference between 0 and 100 points (*p* = .050) and 100 and 1000 points (*p* = .071), but no clear evidence of a difference between 0 and 10 points (*p* = .12*)*. There was strong evidence of a main effect of effort, $F_{(3,51)}$ = 16.38, *p* < .001, n_p^2 = .49. Bonferroni corrected pairwise comparisons revealed evidence of a difference between maximum force exerted on 50% effort trials and all other effort trials (*p*s ≤ .005) and weak evidence of a difference between 100% and 120% effort trials (*p* = .062), but no clear evidence of a difference between other effort trials (*p*s = 1.0). There was no clear evidence of other main effects or interactions (*p*s ≥ .103). There was one outlier, re-running the analysis with this outlier removed did not qualitatively change the findings. Re-running the analysis with age and sex as potential covariates revealed weak evidence of a main effect of sex (*p* = .078) with males exerting a higher maximum force (*M* = 95, *SE* = 3) than females (*M* = 85, *SE* = 4). Re-running the analysis with all participants included (*N* = 25) did not change the findings but a block x reward interaction was revealed (*p* = .016).

Reaction Time. There was strong evidence a main effect of reward, $F_{(1.51,22.65)}$ = 8.91, *p* = .003, n_p^2 = .37, see Figure 2.3. Participants were quicker to respond to higher reward magnitudes: 0 (*M* = 493 ms, *SE* = 25), 10 (*M* = 462 ms, *SE* = 19), 100 (*M* = 463 ms, *SE* = 20) and 1000 (*M* = 442 ms, *SE* = 17) points. Polynomial contrasts revealed evidence that this effect was linear (*p* = .003). Bonferroni corrected pairwise comparisons revealed participants were quicker to respond to 1000 points compared to other points (*p*s ≤ .022) and weak evidence of a difference between 0 and 10 points (*p* = .050). There was no evidence of a difference between other reward magnitudes (*p*s ≥ .31). There was strong evidence of a main effect of block, $F_{(1,15)}$ = 16.30, *p* = .001, n_p^2 = .52. Participants were quicker to respond in the first block (*M* = 450 ms,

SE = 19) compared to the second block (*M* = 481 ms, *SE* = 21). There was evidence of a main effect of effort, $F_{(3,45)} = 4.76$, $p = .006$, $n_p^2 = .24$. Bonferroni corrected pairwise comparisons revealed evidence of a difference in reaction time between 50% and 80% trials (mean difference = 17 ms, $p = .036$) and weak evidence of a difference between 80% and 120% effort trials ($p = .058$). There was no evidence of a difference between other effort trials (ps ≥ .17). There was evidence of an effort x reward interaction, $F_{(3.29, 49.35)} = 4.01$, $p = .01$, $n_p^2 = .21$. There was evidence of a block x effort x reward interaction, $F_{(3.46, 51.96)} = 3.36$, $p = .02$, $n_p^2 = .18$. Re-running the analysis with age and sex as potential covariates revealed evidence of a main effect of sex ($p = .006$): males (431 ms; *N* = 11) had quicker reaction times than females (540 ms; *N* = 5). Re-running the analysis with all participants (*N* = 22) included did not change the findings.

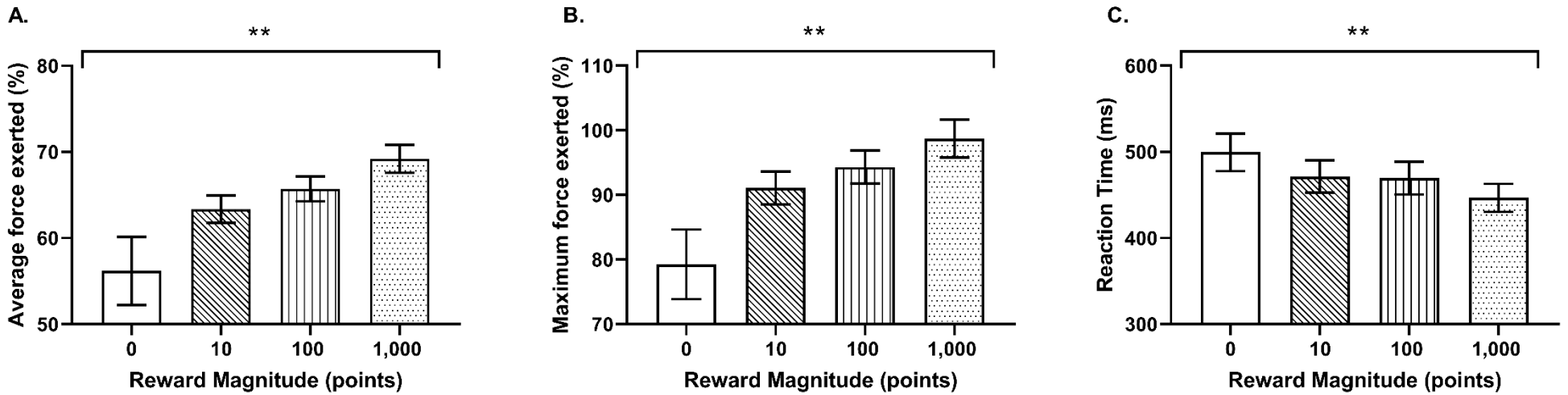

Figure 2.3 Proof-of-concept for the JORT: For higher reward magnitudes, participants exerted a higher average force (A; *N* = 18), maximum force (B; *N* = 18), and were quicker to respond to the target (ms, C; *N* = 16). Error bars represent *SEM*. ** $p < .01$.

2.3.5. Self-report measures

Participant characteristics and distribution of self-report measures appear in Table 2.1.

Table 2.1 Demographic data and questionnaire scores.

Variable	Number	Mean	*SD*
Age	18	21.9	4.0
Beck Depression Inventory-II	17	7.5	5.1
BIS	18	22.2	3.1
BAS Total	18	41.2	4.5
BAS – *drive*	18	11.1	2.3
BAS – *fun seeking*	18	12.6	1.6
BAS – *reward responsiveness*	18	17.6	2.2
CPAS	18	13.3	4.7

Abbreviations: BIS, Behavioural Inhibition System; BAS, Behavioural Activation System; CPAS, Chapman Physical Anhedonia Scale. Note: there was missing data for one participant on the BDI-II due to one question not being answered.

2.3.6. Correlations

To facilitate correlation analyses, individual slopes (force exerted across the four reward magnitudes) were extracted for each participant (as reported in Pfister et al., 2013). There was no clear evidence of a correlation between self-report measures and JORT slopes for relative average force (*p*s ≥ .17), maximum force (*p*s ≥ .12) or reaction time (*p*s ≥ .06). Re-running the analysis with all participants included did not change this finding.

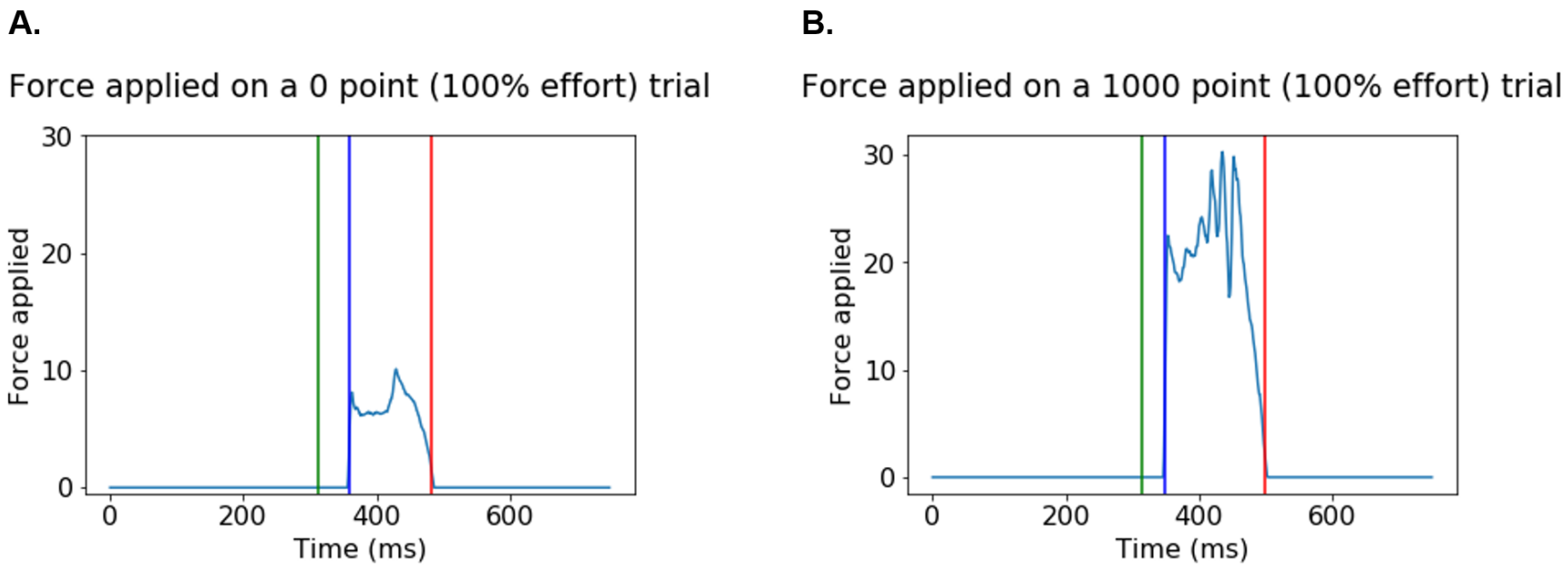

Figure 2.4. Profile of force applied by one participant on their last low (0 point; A) and high (1000 point; B) reward trial which required 100% effort. Green line indicates the time at which target dot appeared, blue line indicates the time at which the participant started to apply force and red line indicates the time at which the target disappeared. *Note*: This is not a representative trial, it is shown for illustrative purposes of a participant who had a positive force slope (i.e., they exerted more force on higher reward trials).

2.4. Discussion

The aim of this chapter was to provide proof-of-concept for a novel reward motivation task in a non-clinical population: the JORT. In this task, participants must push on a force-sensing joystick to chase and catch an onscreen target for different reward amounts. It was predicted that participants will exert more physical force for higher reward trials compared to lower reward trials. Participants did exert a linear increase in physical force (average and maximum force) for higher reward trials. Participants also had a linear decrease in reaction times for higher reward trials. This suggests that this task based purely on physical effort could provide a novel measure of reward motivation.

There are few behavioural tasks that assess reward motivation in humans (see section 1.4.5.1; Dean, 2019). To date, most human studies have measured reward motivation using effort-based decision-making tasks, predominantly using the EEfRT (Dean, 2019; Halahakoon et al., 2020; Lawn et al., 2016). Whilst the EEfRT has revealed important findings in patient populations (Treadway et al., 2012; Yang et al., 2014), a potential confound of this task is its cognitive demands (Bonnelle et al., 2015). In the EEfRT, participants are required to make a decision by weighing up the costs (amount of effort required), benefits (amount of reward on offer) and probability of getting the reward. As a result, it is difficult to ascertain whether deficits in this task reflect impaired reward motivation or instead reflect general cognitive impairments (Bonnelle et al., 2015; J. A. Cooper et al., 2019; Dean, 2019). For example, Whitton and colleagues (2020) found that better working memory using a digit span task predicted increased choice for the high effort/high reward option (on high probability trials) on the EEfRT (Whitton, Merchant, et al., 2020). This is an important consideration for clinical studies as patients may have deficits in cognition (J. A. Cooper et al., 2019). In comparison to the EEfRT, the JORT is a simpler reward motivation task based on physical amount of effort exerted for reward which does not require any explicit decision-making (Bonnelle et al., 2015). Specifically, participants have to exert force on a joystick to catch a target (that will provide them with

reward). Thus, compared to effort-based choice tasks, the simplicity of the JORT means it may provide a more specific measure of physical effort related to reward (Bonnelle et al., 2015).

In the current literature, there are two other behavioural tasks designed to measure the amount of physical effort exerted for reward: the Progressive Ratio Task (PRT) and the handgrip task (Schmidt et al., 2008; as discussed in section 1.4.5.1). Whilst promising, these tasks have not yet been validated to the same degree as the EEfRT and have lacked standardisation across studies. For example, whilst the handgrip task was initially developed to measure physical force exerted for reward (Cléry-Melin et al., 2011; Schmidt et al., 2008), subsequent studies using this task have employed explicit decision-making versions whereby a participant must accept or reject a trial based on the effort required and reward on offer (Bonnelle et al., 2015). Similarly, most versions of the PRT used in the human literature have also included an additional explicit choice (accept or reject a trial). This has resulted in a lack of studies demonstrating validity of the original effort for reward tasks. Additionally, concerns have been raised regarding the potential confounds on the PRT such as temporal discounting and motor ability (Chong et al., 2016). This means that a decreased breakpoint may not reflect a reduced willingness to exert physical effort for reward, but rather intolerance to wait for reward or poorer motor ability (Chong et al., 2016). Therefore, although promising, physical effort for reward tasks that have been used in the literature have not yet been validated to the same degree as effort-based decision-making tasks.

In this study, performance on the JORT did not correlate with self-report measures. In particular, it may be surprising that there was no correlation between the JORT and the BAS, which is designed to measure motivation to approach appetitive outcomes (Carver & White, 1994). However, caution should be taken when interpreting this finding given that the study has a small sample size. Future studies with larger samples will be required to address whether self-report measures of motivation relate to performance on the JORT

2.4.1. Strengths and Limitations

A key strength of this task is its simplicity. Compared to effort-based choice tasks, the JORT has the advantage of being less cognitively demanding. Consequently, performance on this task may better account for potential confounds such as cognitive deficits and cognitive effort impairments (Bonnelle et al., 2015; J. A. Cooper et al., 2019; Dean, 2019). This is particularly important when investigating motivational deficits in patient populations who have impairments in cognitive processing (Chong et al., 2016).

Another strength is that the task accounts for other potential confounds such as delay intolerance. In most tasks (PRT and EEfRT), effort is also associated with an increased delay (time taken to obtain the reward; Pessiglione et al., 2018). This is problematic because reduced performance on the task may not reflect reduced willingness to exert effort, but rather intolerance to delay. An advantage of the JORT is that the time spent on trials is kept roughly the same and therefore performance is less likely to be influenced by temporal discounting.

One limitation of this task is the potential confound of fatigue. As this task is physically demanding, over time participants may exert less effort on the task as a result of fatigue (tiredness), as opposed to reduced motivation. Whilst an important consideration, fatigue could also be of interest when assessing reward motivation in many clinical disorders. For example, some patients may be willing to exert physical effort for reward in normal circumstances but may be less willing once they have already exerted some effort (i.e., reduced motivation may become more apparent as energy is decreased). To check the effects of fatigue on this task, a basic analysis can involve comparing performance between the two blocks of trials. Doing this, we found weak evidence of a main effect of block on average force (p = .047) and strong evidence of a main effect of block on reaction time (p = .001), and thus the effect of block should be considered in future studies. Alternatively, one could also include trial number as a continuous variable in the analysis (Treadway et al., 2012).

The purpose of the calibration phase was to determine a participant's maximum force, which was later used to standardise the amount of effort required on the task. However, many participants (7/25) did not successfully achieve their maximum force during the calibration phase. Possible reasons for this include the lack of visual feedback (the participants received no visual feedback on the force they were exerting on the joystick) and the lack of incentive during the calibration phase. To address this limitation, in subsequent chapters (Chapter 3 and Chapter 5), we altered the calibration such that a person's maximum force was calculated as their peak force reached during the calibration phase *or practice trials* (whichever was highest).

2.4.2. Future Directions

Future studies are needed to validate the JORT as a measure of reward motivation. When developing a new test, there are four quality criteria that must be met: standardisation, sensitivity of task to individual differences, validity (face, construct and predictive), and test-retest reliability (Diederich & Giffroy, 2006). Here, I provide some face validity and in Chapter 3 I provide some construct validity (this task correlates with performance on a different reward motivation task: EEfRT). Further studies are needed to assess test-retest reliability and predictive validity. Specifically, predictive validity could be examined using pharmacological manipulations (such as dopaminergic drugs) and/or examining clinical populations who report deficits in motivation (such as apathy) to examine the tasks sensitivity to detect disease. Validation of behavioural tasks to the same extent as questionnaires is necessary for interpreting results and having a useful measurement tool.

Another area for future research is to incorporate motivation to avoid loss using this task. Here, the task measured motivation to obtain a reward. Arguably, the other side of this coin is motivation to avoid aversive outcomes. Whilst not the focus of this study, future studies could benefit from including avoidance trials whereby participants must push on the joystick to avoid being caught by a pursuing cursor, which would result in them losing points (Perkins et al., 2009). This is particularly relevant

when examining disorders such as apathy, which may not be specific to the reward/pleasure domain. Therefore, assessing aversive motivation alongside reward motivation may provide a more holistic insight into the specific motivation deficits present in patients (specific to reward or a global motivation deficit).

In summary, this study provides proof-of-concept for a novel reward motivation task which provides a simple measure of physical effort expenditure for reward.

Chapter 3: Reward motivation and reward sensitivity in people with high versus low anhedonia

Chapter Aim: Examine different components of reward processing (reward motivation and reward sensitivity) using a battery of behavioural tasks in a non-clinical population with high versus low anhedonia.

Acknowledgements: Steph Suddell, for providing data which enabled the choice of cut-off scores on the SHAPS.

***Note*:** the protocol for this study has been pre-registered on the Open Science Framework (OSF: https://osf.io/p4zt6).

3.1. Introduction

Anhedonia, a markedly diminished interest or pleasure in activities (DSM-5), is a core self-reported symptom of depression that responds poorly to currently available treatments (Uher et al., 2012). Despite its importance, the behavioural and neurobiological basis of anhedonia remains elusive (J. A. Cooper et al., 2018). This may, at least in part, be due to the over-reliance on questionnaires to measure this symptom. Objective measures, particularly those that can be used in both clinical and preclinical research, may improve our mechanistic understanding of anhedonia and aid the development of targeted treatments (Der-Avakian & Markou, 2012; Thomsen, 2015; Treadway & Zald, 2011).

One way to objectively measure anhedonia is behaviourally (see section 1.4.5). Specifically, anhedonia may be due to dysfunction in one or more components of reward processing: motivation to obtain reward ("wanting"), consumption of reward ("liking") and/or learning what predicts reward ("learning") (Berridge & Robinson, 2003; Thomsen, 2015). Despite advancements in preclinical research demonstrating that these components are dissociable (Berridge & Robinson, 1998; Berridge et al., 2009), few studies have tried to dissociate different components of reward in people and relate them to questionnaire measures of anhedonia (McCabe, 2018). It is important to dissociate the precise components related to anhedonia because it may provide an objective biomarker that could be used in the development and testing of new treatments. To aid translational research, translating behavioural tasks from animals to humans may be a promising approach (Der-Avakian et al., 2016).

Although there has been progress in the field of anhedonia and reward processing (see section 1.4.5), there are gaps in the current literature that need to be addressed. First, most studies compare people with depression to healthy controls. Whilst anhedonia is a core symptom of depression, it is possible to have a diagnosis of depression without anhedonia. Therefore, depression and anhedonia should not be used interchangeably. Instead, in line with the RDoC, there is a need for studies to directly measure anhedonia and its severity using anhedonia

questionnaires (Cuthbert, 2014; McCabe, 2018). Second, most studies examine only one component of reward (e.g., motivation) using one task. However, a battery of tasks designed to probe different components of reward (e.g., motivation, sensitivity) in the same population is needed to assess whether these components can be dissociated in people, and whether anhedonia is related to a general reward deficit (dysfunction across components of reward) or is specific to certain domains of reward processing (Husain & Roiser, 2018; Nielson et al., 2020). Third, most human studies examining reward motivation use effort-based decision-making tasks (Halahakoon et al., 2020; Treadway et al., 2009). As preclinical studies commonly measure reward motivation as the amount of physical effort exerted for reward (e.g., PRT), studies should examine whether the amount of physical effort exerted for reward is related to anhedonia. This will enable a more fine-grained understanding of the reward motivation deficits in anhedonia and may inform preclinical research.

3.1.1. Study Aim

To address these gaps, the aim of this study was to examine different components of reward processing (reward motivation and sensitivity) using a battery of behavioural tasks in a non-clinical population who have high versus low symptoms of anhedonia (measured using the SHAPS). Although anhedonia is a clinical symptom, it can be observed to varying degrees in the typical population (Franken et al., 2007). Translational tasks were used to assess effort-based decision-making (EEfRT; Treadway et al., 2009) and reward sensitivity (Sweet Taste Test). This study also included a novel physical effort-for-reward task (JORT; see Chapter 2) to further examine motivational deficits in the absence of explicit decision-making. These tasks were selected based on their potential to dissociate reward components and their potential for cross-species research. All participants also completed multiple self-report measures of anhedonia: SHAPS (Snaith et al., 1995), CPAS (Chapman et al., 1976) and TEPS (Gard et al., 2006). They also completed self-report measures of depression (BDI-II; Beck et al., 1996) and apathy (AES;

Marin et al., 1991). Based on previous literature (section 1.4.5), we predicted that:

H1: In the JORT, compared to individuals with low anhedonia, individuals with high anhedonia, will not exert more force for higher compared to lower reward magnitudes.

H2: In the EEfRT, compared to individuals with low anhedonia, individuals with high anhedonia will make fewer high effort/high reward choices (under 50% probability).

H3: In the Sweet Taste Test, compared to individuals with low anhedonia, individuals with high anhedonia will show a higher detection threshold (i.e., reduced perception).

3.2. Method

3.2.1. Screening

Individuals who scored high (score ≥ 25) or low (score < 18) on the SHAPS in a non-clinical population were invited to take part in this study (based on data from Suddell et al., *unpublished data*). Specifically, these individuals scored in the top and bottom 25th percentile on the SHAPS, which was administered online to 380 volunteers, see Figure 3.1. Due to initial difficulties recruiting, the lower cut-off was increased from a score of < 17 to < 18 (proposed in the pre-registration) on the SHAPS. For a study flow diagram, see Figure 3.2.

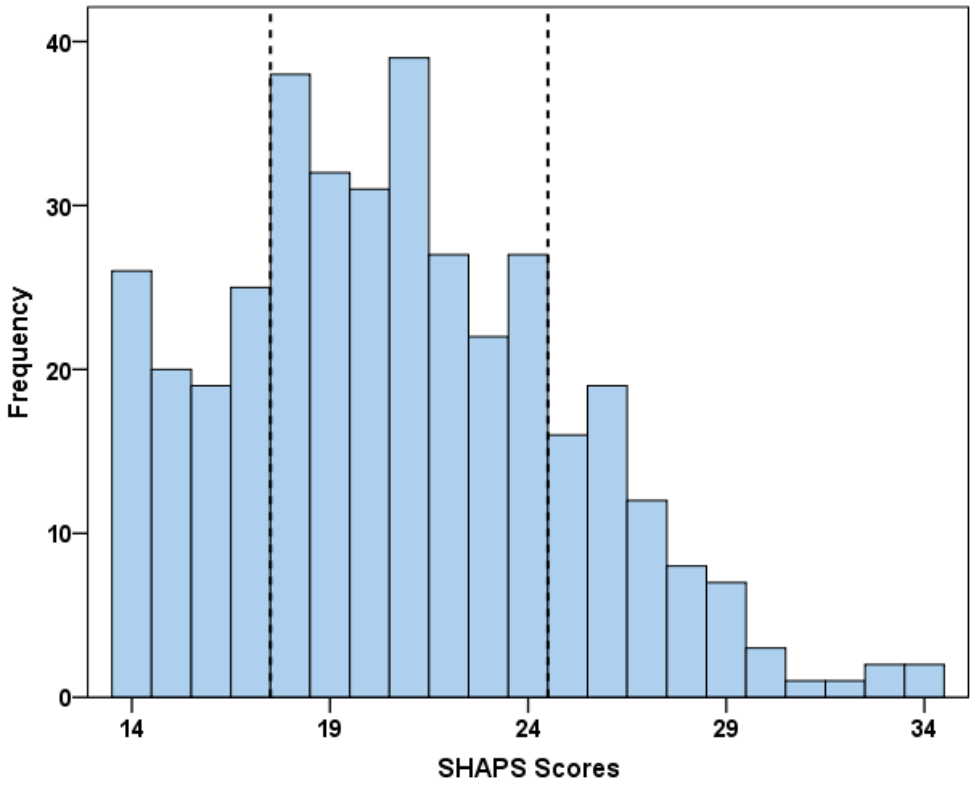

Figure 3.1 Distribution of scores on the SHAPS, dashed lines indicate SHAPS cut-offs (*M* = 20.81, *SD* = 4.4, *N* = 380).

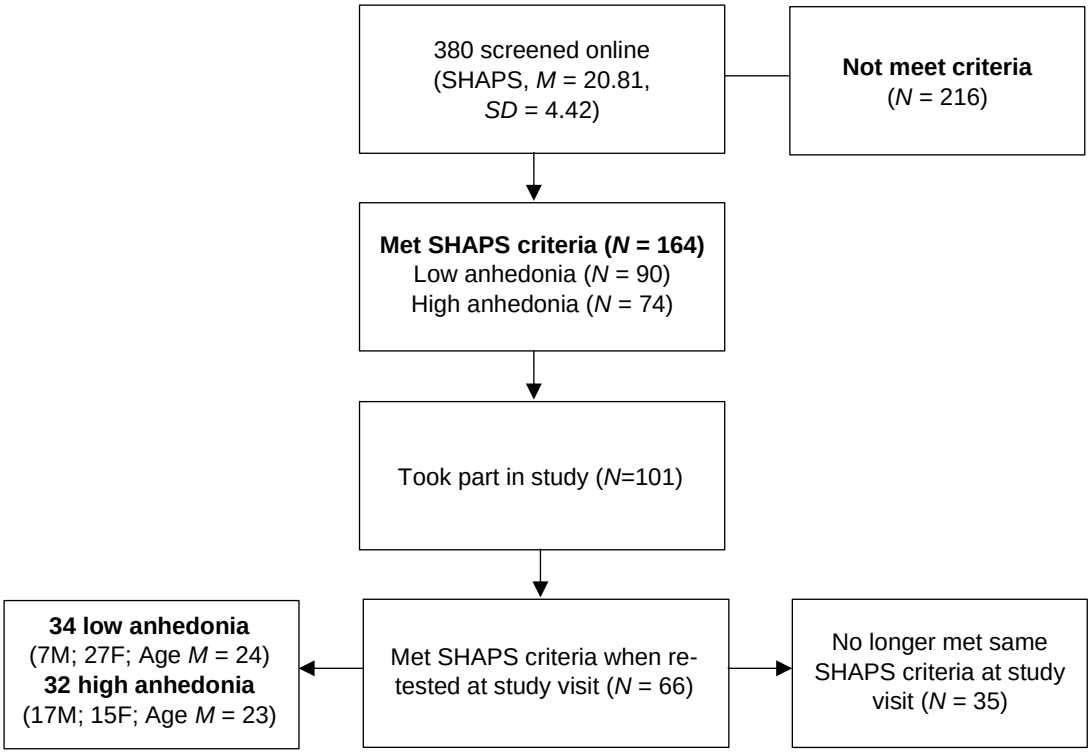

Figure 3.2 Flow diagram of study selection process

3.2.2. Participants

A total of 101 participants (44 low anhedonia, 57 high anhedonia) met the online criteria and took part in this study. Of this group, 66 participants (34 low anhedonia, 32 high anhedonia) still met the SHAPS criteria when re-tested on the SHAPS at the study visit. Only those who still met their criteria (high or low anhedonia) at the study visit were included in the primary analysis.

Participants were recruited using advertisements within the University of Bristol and volunteer databases. Eligibility criteria were: aged ≥ 18 years, fluent in English, not suffering from a mental health condition or neurological illness (self-report), no current physical injuries, no allergy or intolerance to sugar, no disorder of taste or smell, not diabetic, not previously participated in a study using the JORT.

Participants were reimbursed £20 for their time and received an additional performance-based pay (up to £5) based on their performance on one of the two reward motivation tasks (chosen randomly).

Ethics approval was obtained from the Faculty of Biomedical Sciences Research Ethics Committee at the University of Bristol.

3.2.3. Design

This study was a between-participants design. It examined differences in behaviour performance in a non-clinical population with high vs low anhedonia symptoms.

3.2.4. Sample Size Calculation

There were sufficient resources to recruit a target sample size of 66 participants (33/group). Using G*Power 3.1 (Faul et al., 2007), an *a priori* power calculation indicated that 66 participants provided sufficient power (.9) to detect a medium effect (Cohen's f = .25) at alpha = .05 with correlations among repeated measures (0.5) and non-sphericity correction (0.3334) (ANOVA: repeated measures, within-between interaction; based on the JORT). Given that we had limited information that enabled the estimation of an effect size, the results should be

interpreted with appropriate caution given the possibility that the study is underpowered. Whilst the target sample size was 66, four participants were excluded from the JORT analysis (based on *a prior* criteria) resulting in an achieved sample size of 62 participants (33 low anhedonia, 29 high anhedonia).

3.2.5. Behavioural Measures

Joystick-Operated Reward Runway Task (JORT)

See chapter 2 for task details. The only difference between studies was how the maximum calibrated force was calculated. In this study, maximum calibrated force was calculated as the peak force exerted on the calibration *or practice trials*. This was done to reduce the number of participants successfully achieving more than 75% of trials and thus being excluded. This reduced the proportion of participants achieving over 75% trials: chapter 2 (28% participants) vs current study (6% participants). This criterion (> 75% trials achieved) was chosen because these participants must have achieved trials that were designed to be impossible, suggesting that they did not successfully reach their maximum force during the calibration phase.

Effort Expenditure for Reward Task (EEfRT)

The EEfRT measures effort-based decision making (Treadway et al., 2009). On each trial, participants are given a choice between an "easy" and "hard" task. In the hard task, participants must do 98 button presses within 21 seconds (using the little finger on their non-dominant hand) for 58p - £2, see Figure 3.3. In the easy task, participants must do 30 button presses (using the index finger on their dominant hand) within 7 seconds for 50p. They have 5 seconds to make a choice, or they are randomly assigned to either task. Each trial also contains a probability cue which indicates the probability of winning money if they successfully complete the trial (referred to as "win trials"): 12%, 50% or 88%. This probability applies to both the easy and hard choices. There are an equal proportion of each probability across the experiment. Participants are told that two "win trials" may be paid to them at the end of the experiment (i.e.,

performance-based pay). All participants complete the trials in the same pre-randomised order.

Prior to the task, participants are given standardised verbal and written instructions (as provided by Treadway et al., 2009). Following this, all participants complete three trials to assess their motor ability (i.e., finger tapping rate) where they press a button with the little finger of their non-dominant hand for 21 seconds as fast as possible. This is done to determine figure tapping speed (i.e., the average number of button presses across the three trials). Following this, participants complete four practice trials.

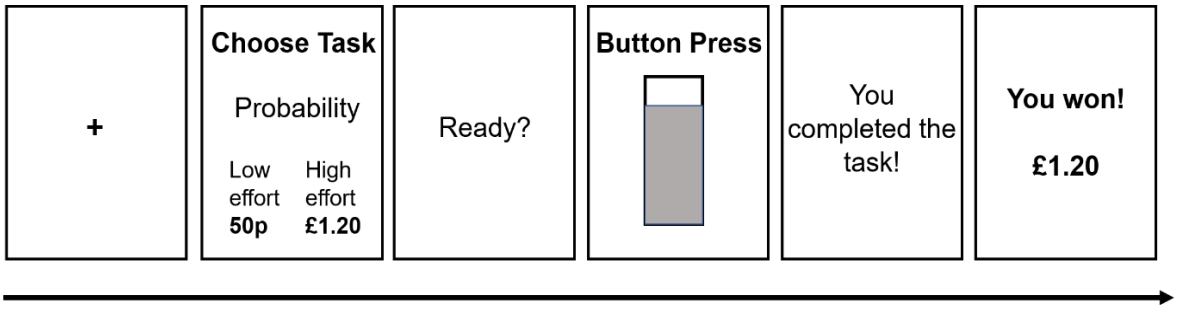

Figure 3.3 Example trial on the Effort Expenditure for Rewards Task (EEfRT): fixation cross (1 s), choice period where the participant is informed about the probability of the trial being a "win trial" and reward magnitude of the hard task (5 s), "Ready" screen (1 s), button pressing (7 s easy task or 21 s hard task), feedback as to whether the participant successfully completed the task followed by feedback as to whether they received money for that trial (Treadway et al., 2009).

The only difference between the original task and this task is that I modified the payment in pounds such that the easy trial was worth 50p and the maximum amount on offer for the hard trial was £2. Nevertheless, the proportion of money on offer on each trial was approximately the same as the original task. The primary outcome in this task is proportion of hard-task choices.

Sweet Taste Test

A modified version of the Sweet Taste Test (Berlin et al., 1998) was used to measure threshold to detect sucrose. Here, on each trial, participants were given a concentration of sucrose delivered in 15 mL of water and

were asked to sip one mouthful of the solution, swish it around their mouth for approximately 5 seconds and then spit out the solution (Berlin et al., 1998). Following this, the participant was asked if they could detect the presence of sugar in the solution (Berlin et al., 1998). In between trials, participants were asked to sip one mouthful of water, swish it around their mouth for approximately 5 seconds and then spit this out. Prior to the task, participants were asked to complete two practice trials containing water. This was done to ensure that the participant was familiar with the procedure and to clean their palette. Seven concentrations of sugar were used (0, 0.5, 1, 1.5, 2, 2.5, 5% w/v). A staircase method was employed which included five reversals. The first concentration administered was always the strongest concentration (i.e., 5% sucrose) to ensure participants were aware of what to detect. A staircase method was used as it provides a fast determination of threshold. The detection threshold was calculated as the mean of the five boundaries (i.e., points at which they changed response from either detect to fail to detect or vice versa).

3.2.6. Self-Report Measures

Snaith Hamilton Pleasure Scale (SHAPS)

The SHAPS (Snaith et al., 1995) is used as the primary measure of hedonic capacity in this study. It was administered during screening (online) and re-administered at the study visit. This is a 14-item questionnaire with a 4-point scale. It asks participants to report their ability to experience pleasure in the last few days (e.g., smell of freshly baked bread, being with family). A cut-off of > 2 has been suggested to provide the "best discrimination of normal and abnormal" (Snaith et al., 1995). Whilst the original scoring algorithm coded each item as dichotomous, recent approaches have used continuous coding (each item scored as 1 - 4) to increase dispersion of the data (Franken et al., 2007). The psychometric properties of this continuous version have been supported (Franken et al., 2007): it has displayed adequate test-retest reliability over a 3-week interval (r = .70), internal consistency (a = .91; Franken et al., 2007) and good convergent validity with other pleasure

scales (Leventhal et al., 2006). I originally included the SHAPS as reported in the original paper (Snaith et al., 1995). However, due to poor test-retest reliability, I later changed the order or responses to be consistent (i.e., strongly agree as the top response for all questions).

Chapman Physical Anhedonia Scale (CPAS)

The CPAS (Chapman et al., 1976) is used as a measure of trait anhedonia. Higher scores indicate higher trait anhedonia. See Chapter 2 for more details.

Temporal Experience of Pleasure Scale (TEPS)

The TEPS (Gard et al., 2006) aims to dissociate consummatory and anticipatory anhedonia. It contains two subscales which assess anticipatory (10-items) and consummatory (8-items) anhedonia on a 6-point scale. Due to its recent development, this questionnaire has limited psychometric testing (Gard et al., 2006; Rizvi et al., 2016). Nevertheless, it does appear to have good test-retest reliability (over a mean interval of 6 weeks; r = .75 to .81), satisfactory convergent validity (FCPS and CPAS) and high discriminant validity (BDI) in a student population (Gard et al., 2006). Unlike other questionnaires, higher scores on the TEPS indicate lower levels of anhedonia.

Beck Depression Inventory (BDI-II)

The BDI-II (Beck et al., 1996) is used to measure symptoms of depression. Higher scores indicate increased symptoms of depression. See chapter 2 for more details.

Apathy Evaluation Scale (AES)

The AES (Marin et al., 1991) is an 18-item self-report questionnaire on a 4-point scale which ranges from "Not at all True" to "Very True". Scores range from 18-72, with higher scores indicating increased apathy symptoms. It has good test-retest reliability over a mean interval of 25 days (r = .76; Marin et al., 1991). The self-reported version also has good convergent validity with the clinician-rated apathy version (r = .72)

and some discriminant validity from self-reported depression (r = .42; Marin et al., 1991).

Other information

All participants provided demographic information (age, sex). Participants also answered questions regarding: smoking status ("do you currently smoke tobacco?"; 3 levels: yes daily, yes less than daily, not at all), income band (3 levels: low, medium, high) and financial worries (2 levels: yes or no). Questions also had the option "prefer not to say".

3.2.7. Procedure

Interested participants were sent the information sheet via email and asked to complete the online screening questionnaire – SHAPS (Snaith et al., 1995). Those who met the eligibility and screening criteria were invited to attend a two-hour test session at the University of Bristol.

Upon arrival at the test session, participants provided written informed consent. All participants were tested individually. Participants completed the behavioural tasks in the following order: EEfRT, JORT and the Sweet Taste Test; which took approximately one hour. Participants then completed self-report measures: demographic form, SHAPS, CPAS, TEPS, BDI-II, AES. Upon completion, all participants were verbally debriefed.

3.2.8. Data analyses

Analyses were performed in SPSS 24 (IBM). Primary analyses were run on those who met the SHAPS cut-offs at the study visit (N = 66). Based on previous research, *a priori* potential co-variates were examined and their main effects retained in each model (Engqvist, 2005).

3.2.8.1. Primary Analyses

For the JORT, 2 x 4 mixed ANOVAs were conducted to examine differences between groups in relative average force, maximum force, and reaction time. The between-subjects factor was group (2 levels: high vs low anhedonia). The within-subject's factor was reward (4 levels: 0,

10, 100, 1000 points). Data were collapsed across effort and block, although analyses were also re-run as a full ANOVA (including block and effort) to explore any potential interactions with group. The primary outcome was relative average force.

For the EEfRT, 2 x 3 mixed ANCOVAs were conducted to examine differences between groups in mean proportion of hard-task choices and reaction time. The between-subjects factor was group (2 levels: high and low anhedonia). The within-subjects factor was probability (3 levels: 12%, 50%, 88%). Sex was included as a potential co-variate based on previous literature (Treadway et al., 2009). The primary outcome was mean proportion of hard-task choices.

For the Sweet Taste Test, a univariate ANCOVA was conducted to examine differences between groups in detection threshold. Smoking status (3 levels: daily, less than daily, not at all) was included in the analysis as a potential co-variate based on previous literature (Sato et al., 2002).

Data were checked for normality (using Kolmogorov-Smirnov and histograms), homogeneity of variances (Levene's) and potential outliers were examined via boxplots (scores 3 times greater than the interquartile range in any condition). Where there were substantial deviations from normality or heterogeneity of variances between groups, analysis was conducted on log transformed data (or square root transformed if 0 values were present) only if this corrected the assumptions. Greenhouse-Geiser statistics corrections were applied where Mauchly's Test of Sphericity was $p < .05$. Sensitivity analysis with any statistical outliers excluded was conducted. Data are presented with all participants retained in the analysis. Where removal of outliers substantially affected the findings, results are also reported with outliers excluded. All post-hoc comparisons were Bonferroni-corrected. Partial eta-squared (n_p^2) is reported as the effect size.

3.2.8.2. Exploratory Analyses

Correlations. Associations between performance on reward processing tasks and self-report measures of anhedonia, depression and apathy were

run using Spearman's correlation (N = 101), due to non-normality of some variables. Additional Spearman's correlations were run to investigate associations between behavioural tasks. As these were exploratory, no corrections for multiple comparisons were used.

Generalised Estimating Equation (GEE) models (Zeger & Liang, 1986). To further assess the replicability of the results of Treadway et al. (2009), additional GEE models were applied to the EEfRT data. GEE models focus on data from individual trials (i.e., trial-level approach) rather than summary statistics (i.e., subject-level approach; Bryant et al., 2017; Wardle et al., 2011). In the EEfRT, this enables the inclusion of fixed parameters (e.g., anhedonia score), time-varying categorical parameters (e.g., probability: 12, 50, 88) *and time-varying continuous parameters* (e.g., reward magnitude of the hard-task choice)(Yang et al., 2014). GEEs also allow trial number to be included as a covariate to control for the effect of fatigue on choice (Treadway et al., 2012). An additional advantage of GEEs is that compared to general linear models (GLM; e.g., ANOVA), GEE models have less strict assumptions: (1) they do not require the dependent variable to be normally distributed and (2) they allow for correlated responses within a subject (see Ballinger, 2004 for a review). Overall, this enables GEE models to have increased power to detect effects compared to GLMs and may provide less biased parameter estimates (Ballinger, 2004; Lawn et al., 2016).

Consistent with Treadway and colleagues (2009), the dependent variable was choice (binary outcome: easy or hard) and therefore a binary logistic model was employed. We also used an unstructured working correlation matrix (as reported in Treadway et al., 2009). All GEE models include: trial number, probability, reward magnitude (reward on offer for hard-task choice), expected value (reward magnitude x probability) and trait anhedonia (score on CPAS; Treadway et al., 2009). The within-subjects factor was trial number (McCarthy et al., 2016). The quasi likelihood under independence model criterion (QIC) is used for model comparison (Pan, 2001).

3.3. Results

3.3.1. Descriptive

For participant characteristics and demographics, see Table 3.1.

Table 3.1 Demographic data and questionnaire scores for participants in the high and low anhedonia group

	Low Group		High Group		Group Difference		
	Mean	*SD*	Mean	*SD*	*F*	*p-value*	Post-hoc
Age	24.0	5.1	22.8	8.6	.41	.52	n/a
Males (*N*)	7	21%	17	53%	$X^2 = 7.54$	.006	H > L
Smoke Status	2.7	0.7	2.7	0.6	$X^2 = .23$	.89	n/a
Income	2.3	0.6	2.2	0.6	$X^2 = .64$	.73	n/a
Money Concern	12	36%	16	50%	$X^2 = 1.23$	.27	n/a
SHAPS	15.4	1.0	27.6	2.2	838.34	<.001	H > L
CPAS	9.6	5.7	18.0	7.1	27.67	<.001	H > L
TEPS – A	50.5	4.6	40.3	5.2	71.10	<.001	L > H
TEPS – C	40.6	5.3	30.3	6.2	52.80	<.001	L > H
BDI-II	6.4	5.5	11.4	7.6	9.41	.003	H > L
Apathy Scale	24.6	4.4	32.4	6.2	33.74	<.001	H > L

Abbreviations: current smoke status (1=daily,2=less than daily, 3=not at all); income (1=high…3=low); money concern, participants who reported yes to finance concerns; SHAPS, Snaith-Hamilton Pleasure Scale; TEPS, Temporal Experience of Pleasure Scale (A, anticipatory; C, consummatory); BDI-II, Beck Depression Inventory-II; n/a, not applicable. Welch's ANOVA and Chi Square run to compare groups.

3.3.2. Primary Analyses

3.3.2.1. Joystick-Operated Reward Runway Task

Four participants achieved over 75% trials and were excluded from the analysis. In total, 62 participants (33 low anhedonia, 29 high anhedonia) were included in the analysis.

Data assumptions. For all outcomes, residuals for some trial types were not normally distributed (2/8). Transformations either did not improve normality (average and maximum force) or weakened homogeneity of variances (reaction time) and so analysis was done on non-transformed data. No outliers were identified for average or maximum force, one was identified for reaction time.

Average force. There was strong evidence of a main effect of reward $F_{(1.45,87.14)} = 39.41$, $p < .001$, $n_p^2 = .40$. Participants exerted more force for higher reward magnitudes: 0 points ($M = 51.79$, $SE = 2.05$), 10 points ($M = 60.34$, $SE = 1.52$), 100 points ($M = 64.09$, $SE = 1.16$) and 1000 ($M = 66.48$, $SE = 1.12$) points. Bonferroni-corrected pairwise comparisons revealed strong evidence of a difference between all reward magnitudes (ps ≤ .003). There was no evidence of a main effect of group ($F_{(1,60)} = .004$, $p = .95$, $n_p^2 < .001$; see Figure 3.4) or reward x group interaction ($F_{(1.45,87.14)} = .56$, $p = .52$, $n_p^2 = .009$).

Maximum force. There was strong evidence of a main effect of reward $F_{(1.47,88.08)} = 36.85$, $p < .001$, $n_p^2 = .38$. Participants exerted a higher maximum force for higher reward magnitudes: 0 points ($M = 73.90$, $SE = 3.00$), 10 points ($M = 85.86$, $SE = 2.38$), 100 points ($M = 91.16$, $SE = 1.91$) and 1000 points ($M = 94.08$, $SE = 1.89$). Bonferroni-corrected pairwise comparisons revealed evidence of differences between all reward magnitudes (ps ≤ .006). There was no evidence of a main effect of group ($F_{(1, 60)} = .49$, $p = .49$, $n_p^2 = .008$; see Figure 3.4) or reward x group interaction ($F_{(1.47,88.08)} = .67$, $p = .47$, $n_p^2 = .011$).

Reaction time. There was strong evidence of a main effect of reward, $F_{(1.18,70.73)} = 13.90$, $p < .001$, $n_p^2 = .19$. Participants were quicker to respond to higher reward magnitudes: 0 points ($M = 520$ ms, $SE = 15$),

10 points (*M* = 477 ms, *SE* = 11), 100 points (*M* = 479 ms, *SE* = 11) and 1000 points (*M* = 468 ms, *SE* = 11). Bonferroni-corrected pairwise comparisons revealed evidence of a difference between all reward magnitudes (*p*s ≤ .024), except between 10 and 100 points (*p* = 1.0). There was no evidence of a main effect of group ($F_{(1,60)}$ = .86, *p* = .36, n_p^2 =.014; see Figure 3.4) or reward x group interaction ($F_{(1.18,70.73)}$ = .049, *p* = .86, n^2_p = .001). There was one outlier that, when removed, did not change the findings overall but did strengthen the reward x group interaction, $F_{(1.97,116.10)}$ = 2.30, *p* =.106, n_p^2 = .04. Note that re-running the analysis including sex as a covariate revealed strong evidence of a main effect of sex, $F_{(1,59)}$ = 13.98, *p* < .001, n_p^2 = .19, with males being quicker to respond (*M* = 433 ms, *SE* = 17; *N* = 21) than females (*M* = 515 ms, *SE* = 12; *N* = 41). Re-running the analysis with sex included in the model did not alter the lack of evidence of a main effect or interaction with group.

Re-running all analyses (average force, maximum force, and reaction time) as full 2*4*4 ANOVAs still did not reveal any evidence of a main effect of group or interactions with group (*ps* ≥ .18).

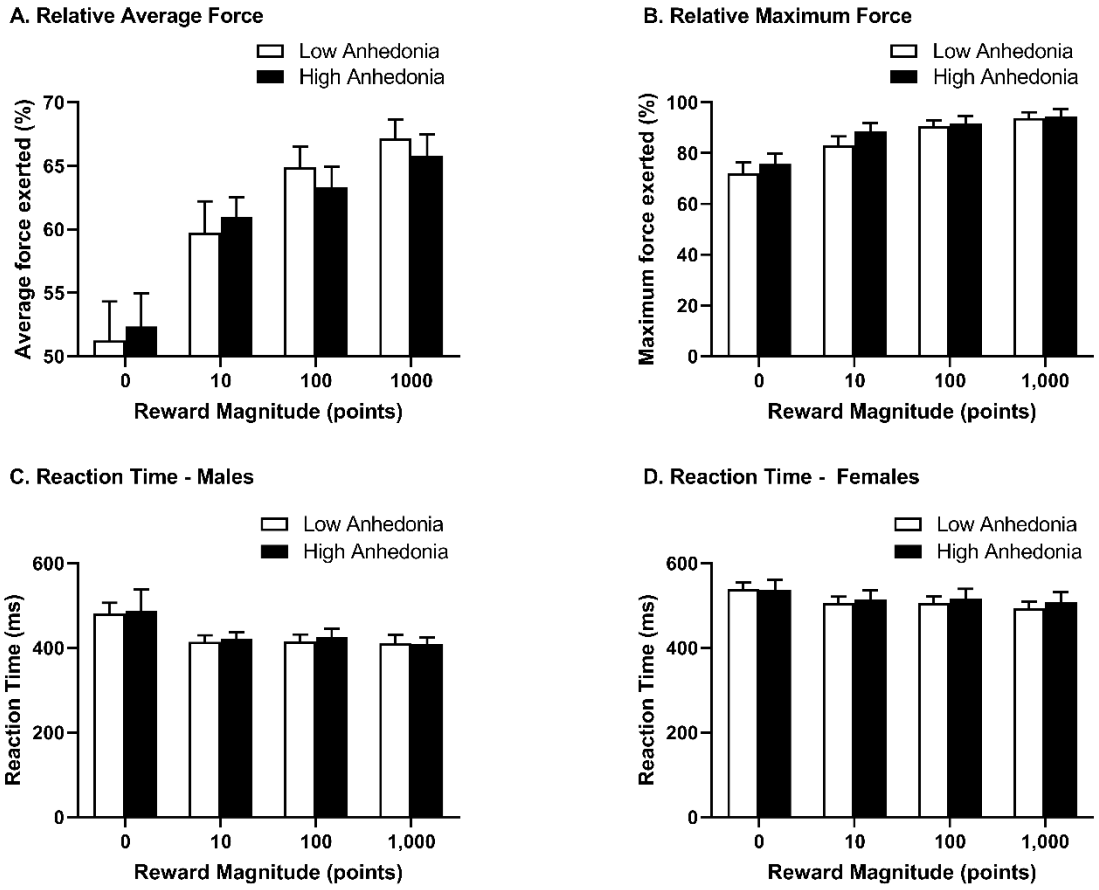

Figure 3.4. Differences between the high and low anhedonia group on the JORT for: (A) relative average force (*N* = 33 low, 29 high), (B) maximum force (*N* = 33 low, 29 high) and (C,D) reaction time (ms). As there was evidence of a sex difference in reaction time on the JORT ($p < .001$), data are presented separately for (C) males (*N* = 6 low, 15 high) and (D) females (*N* = 27 low, 14 high). Error bars represent *SEM*.

3.3.2.2. Effort Expenditure for Reward Task

Consistent with Treadway (2009), only the first 50 trials were used. Trials in which the participant did not make a choice within the time limit were not included in the analysis (*M* = 49.20, *SD* = 1.90, range = 39 to 50).

Data assumptions. For proportion of hard-task choices, there was heterogeneity of variances between groups for low probability trials ($p = .009$) and non-normality for the low probability ($ps < .001$) and high probability for the high group ($p = .03$). Transformations improved the assumption of homogeneity of variances but worsened normality. Based

on this, analysis is done on non-transformed data. One outlier was identified for proportion of hard task choices, none were identified for reaction time.

Proportion of hard task choices. There was strong evidence of a main effect of probability, $F_{(2,126)} = 209.12$, $p < .001$, $n_p^2 = .77$. Participants chose the hard-task choice more often when the probability of winning was higher: low ($M = 9.68$, $SE = 1.82$), medium ($M = 31.12$, $SE = 2.39$) and high ($M = 57.14$, $SE = 2.37$). Bonferroni-corrected pairwise comparisons revealed evidence of a difference between all probabilities ($ps < .001$). There was evidence of a main effect of group, $F_{(1,63)} = 4.45$, $p = .039$, $n_p^2 = .066$, the higher anhedonia group ($M = 28.9$, $SE = 2.4$) chose the hard-task choice less often than the low anhedonia group ($M = 36.4$, $SE = 2.6$; see Figure 3.5). There was no evidence of other main effects or interactions ($ps \geq .57$). However, removal of the outlier weakened the evidence of a main effect of group, $F_{(1,62)} = 2.64$, $p = .109$, $n_p^2 = .041$). *Post-hoc* Mann-Whitney *U* tests revealed evidence of a difference between groups on low probability trials ($p = .045$), but this did not survive Bonferroni corrections for multiple comparisons. There was no evidence of a difference between groups on medium or high probability trials ($ps \geq .28$).

Reaction time. There was strong evidence of a main effect of probability, $F_{(2,126)} = 17.91$, $p < .001$, $n_p^2 = .22$, see Figure 3.5. Participants were quicker to make a choice when there was a low probability of winning money: 12% ($M = 1.72$ seconds, $SE = .06$), 50% ($M = 1.93$ seconds, $SE = .07$) and 88% probability trials ($M = 1.92$ seconds, $SE = 0.07$). Bonferroni-corrected comparisons revealed evidence of a difference between probability levels ($ps < .001$), except medium and high probability ($p = .1$). There was no clear evidence of other main effects or interactions ($ps \geq .21$).

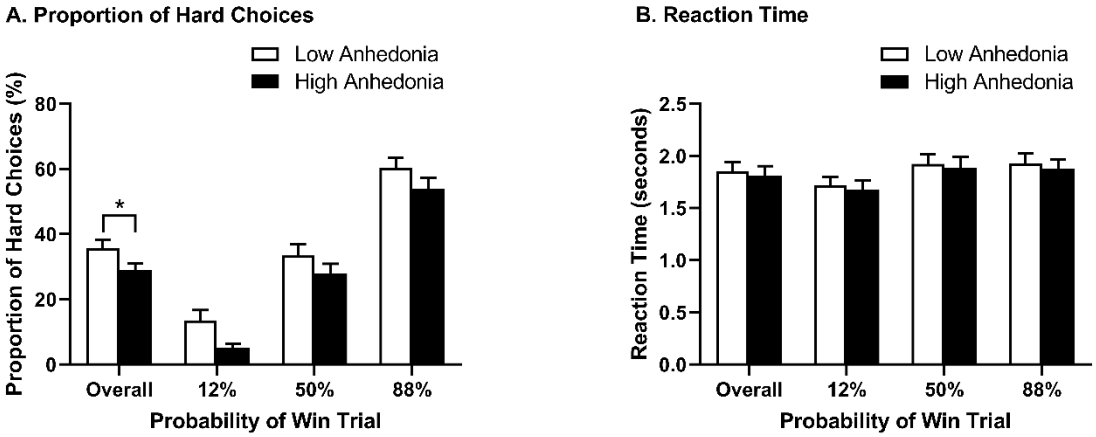

Figure 3.5 Difference between the high and low anhedonia group on the EEfRT across different probability levels: mean proportion of hard task-choices (A) and reaction time (B). *N* = 34 low and 32 high anhedonia. Error bars represent *SEM.*

Finger tapping speed. There was no evidence of a difference between the high (*M* = 98.54, *SD* = 9.49) and low (*M* = 97.23, *SD* = 9.92) anhedonia group in finger tapping speed prior to the task, $t_{(64)}$ = -.55, *p* = .58. Additionally, there was no evidence of a clear difference between groups in mean button pressing rate (i.e., button pressing speed) for the easy or hard task choices (*p*s ≥ .11). This suggests that any reduced proportion of hard-task choice in the high anhedonia group cannot be attributed to reduced motor ability.

Trials completed. The mean percent of trials completed was 97.7% (*SD* = 4.8, range = 72 – 100%). Additionally, I checked the number of participants who only chose the easy or hard-task to confirm that these participants did not drive the findings. In total, one participant only chose the easy task and there were no participants who only chose the hard task. Removal of this participant weakened the evidence of a main effect of group (*p* = .051).

3.3.2.3. Sweet Taste Test

Based on *a priori* criteria, participants who reported detection of sugar in 0% sugar concentrations were excluded as the detection boundary could

not be calculated. This excluded 5 participants. In total, 61 participants (31 low anhedonia, 30 high anhedonia) were included in the analysis.

Analysis was done on log transformed data, which then met the assumption of normality. There was evidence of a main effect of group, $F_{(1,57)} = 4.56$, $p = .037$, $n_p^2 = .07$. The high anhedonia group required a higher concentration of sucrose to detect its presence compared to the low anhedonia group, see Figure 3.6. Removing one outlier strengthened the evidence of a main effect of Group ($p = .015$, $n_p^2 = .10$). Interestingly, further investigation of this outlier revealed that this participant scored the highest on the apathy scale in the low anhedonia group (AES score = 38). The evidence of a main effect of group did not differ when run on non-transformed data ($p = .020$) or using a non-parametric Mann-Whitney *U* test with the covariate excluded ($p = .016$). There was no evidence of a main effect of smoking status, $F_{(2,57)} = .41$, $p = .66$, $n_p^2 = .014$.

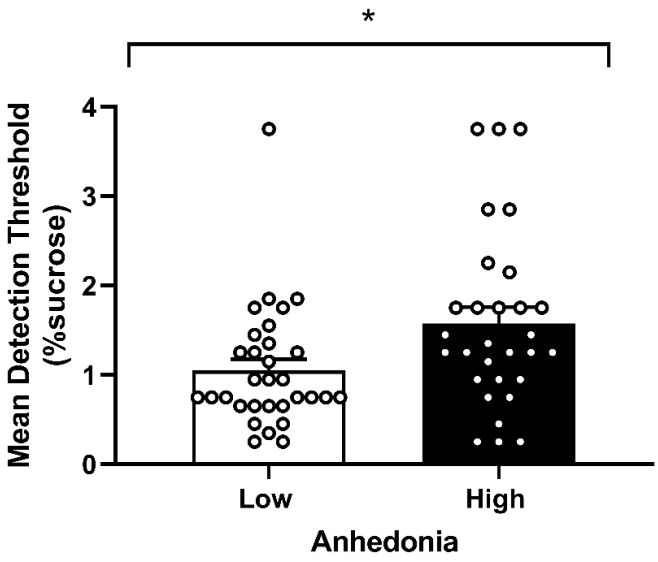

Figure 3.6. Difference between the high and low anhedonia group in the Sweet Taste Test. Individual points represent individual participants. *N* = 31 low and 30 high anhedonia. Error bars represent *SEM.*

3.3.3. Exploratory Analyses

3.3.3.1. Descriptive Statistics

In total, 101 participants were included in the analysis. There was missing data for some self-report measures, see Table 3.2. For correlations between self-report measures, see Table 3.3.

Table 3.2. Distribution of scores on self-report measures.

Variable	Number	Mean	*SD*
SHAPS	101	21.4	5.6
CPAS	100	12.6	7.3
TEPS – Anticipatory	100	45.6	7.2
TEPS – Consummatory	101	36.6	7.0
Beck Depression Inventory-II	100	8.9	6.8
Apathy Evaluation Scale (AES)	100	28.6	6.1

Abbreviations: SHAPS, Snaith-Hamilton Pleasure Scale; CPAS, Chapman Physical Anhedonia Scale; TEPS, Temporal Experience of Pleasure Scale. Note: missing data (*N* = 1) for CPAS, TEPS-Anticipatory, BDI-II and AES where a participant either recorded more than one response to a question or missed a question.

Table 3.3. Correlations between self-report measures.

	SHAPS	CPAS	TEPS-A	TEPS-C	BDI-II	AES
SHAPS		.43**	-.58**	-.58**	.29**	.49**
CPAS			-.52**	-.67**	.28**	.48**
TEPS – A				.65**	-.26**	-.42**
TEPS – C					-.27**	-.53**
BDI-II						.47**

Spearman's rho, *N* = 99 - 101, *<.05, **<.01. Anhedonia scales: SHAPS, CPAS, TEPS (A, anticipatory; C, consummatory). Depression scale: BDI-II. Apathy scale: AES.

3.3.3.2. Correlations between tasks and self-report measures

In line with the original findings of the EEfRT, there was evidence of a negative correlation between trait anhedonia (CPAS) and proportion of hard-task choices ($r_{(100)}$ = -.29, p = .003; see Table 3.4), which was observed across all probability levels (ps ≤ .028). On low probability trials, there was also evidence of a correlation between hard-task choice and the anticipatory scale on the TEPS ($r_{(100)}$ = .21, p =.039) and the SHAPS ($r_{(101)}$ = -.21, p = .036).

In the Sweet Taste Test, there was evidence of a positive correlation between mean detection threshold and symptoms of depression (BDI-II; $r_{(92)}$ = .27, p =.010), anhedonia (SHAPS: $r_{(92)}$ = .27, p = .008; CPAS: $r_{(91)}$ = .22, p = .033), and apathy (AES; $r_{(91)}$ = .23, p = .026; see Table 3.4), and weaker evidence with the TEPS-CON ($r_{(92)}$ = -.19, p = .076). Participants who had higher symptoms of depression, apathy and anhedonia required a higher concentration of sucrose to detect its presence, see Table 3.4.

In the JORT, to facilitate correlation analyses, individual slopes (force exerted across the four reward magnitudes) were extracted for each participant (Pfister et al., 2013). There was no clear evidence of a correlation between self-report measures and the JORT, see Table 3.4.

Table 3.4. Spearman's correlations between behavioural tasks and questionnaires.

Variable		JORT	EEfRT	STT
SHAPS	*R*	-.09	-.14	**.27****
	p-value	.38	.16	.008
CPAS	*R*	-.03	**-.29****	**.22***
	p-value	.79	.003	.033
TEPS–A	*R*	.001	.16	-.15
	p-value	.99	.12	.17
TEPS–C	*R*	-.07	.09	-.19
	p-value	.50	.39	.076
BDI-II	*R*	-.04	-.06	**.27***
	p-value	.70	.55	.010
Apathy Scale	*R*	.01	-.04	**.23***
	p-value	.91	.66	.026

Abbreviations: STT, Sweet Taste Test - mean detection threshold; EEfRT, Effort Expenditure for Reward Task – overall proportion of hard task choices; JORT, Joystick Operated Runway Task – slope of average force across the four reward magnitudes; SHAPS, Snaith Hamilton Pleasure Scale; CPAS, Revised Chapman Physical Anhedonia Scale; TEPS, Temporal Experience of Pleasure Scale (A, Anticipatory; C, Consummatory); BDI-II, Beck Depression Inventory II; Apathy Scale, Apathy Evaluation Scale. *N* = 91–101.

3.3.3.3. Correlations between tasks

There was evidence of a positive correlation between proportion of hard-task choices on the EEfRT and average force slopes on the JORT, $r_{(101)}$ = .21, p = .039, participants who were more willing to choose the high effort/high reward option exerted more force for higher compared to lower reward magnitudes on the JORT. There was no evidence of a correlation between the EEfRT and Sweet Taste Test (p = .84) or JORT and Sweet Taste Test (p = .49).

3.3.3.4. GEE models for the EEfRT

The first model examined the main effect of reward magnitude, probability, expected value and trait anhedonia (measured using the CPAS). This model found evidence that reward magnitude and expected value were positive predictors of hard-task choice and trial number was a

negative predictor of hard-task choice. There was also some weak evidence that the CPAS was a negative predictor of hard-task choice and probability was a positive predictor of hard-task choice. These findings are consistent with Treadway et al. (2009), who reported all parameters to be predictors of hard-task choice.

Models 2, 3 and 4 tested for an interaction between trait anhedonia (CPAS score) and: probability (model 2), reward magnitude (model 3) and expected value (model 3). There was no evidence that any of these interactions predicted hard-task choice. See Table 3.5 for all GEE models.

Table 3.5. GEE models for the EEfRT.

		B	*SE*	95% WALD CI	*P*	QIC
MODEL 1						4560.96
	Trial Number	-.013	.00	-.022 to -.005	.002	
	Probability	1.099	.62	-.114 to 2.312	.076	
	Reward	1.061	.35	.381 to 1.740	.002	
	Expected Value	2.597	.45	1.718 to 3.477	<.001	
	CPAS	-.031	.02	-.064 to .002	.063	
MODEL 2						4563.03
	Trial Number	-.014	.00	-.022 to -.005	.002	
	Probability	1.003	.74	-.445 to 2.452	.174	
	Reward	1.066	.36	.369 to 1.763	.003	
	Expected Value	2.60	.46	1.705 to 3.494	<.001	
	CPAS	-.037	.02	-.071 to -.002	.036	
	CPAS x Probability	.009	.03	-.058 to .076	.797	
MODEL 3						4559.79
	Trial Number	-.013	.00	-.022 to -.005	.002	
	Probability	1.063	.58	-.067 to 2.193	.065	
	Reward	1.173	.49	.218 to 2.127	.016	
	Expected Value	2.638	.41	1.826 to 3.450	<.001	
	CPAS	-.018	.04	-.102 to .065	.666	
	CPAS x Reward	-.013	.03	-.066 to .040	.625	
MODEL 4						4748.22
	Trial Number	-.005	.00	-.012 to .002	.152	
	Probability	1.043	.62	-.164 to 2.251	.090	
	Reward	.657	.35	-.026 to 1.340	.059	
	Expected Value	3.890	1.09	1.749 to 6.031	<.001	
	CPAS	-.011	.03	-.074 to .052	.734	
	CPAS x Expected Value	-.072	.05	-.171 to .026	.151	

3.4. Discussion

Using a battery of tasks, this study found that different components of reward may be dissociable in people, as demonstrated by the lack of correlations between tasks. In relation to anhedonia (measured using the SHAPS), there was no clear evidence of a difference between the high and low anhedonia group in physical effort exerted for reward (JORT). However, compared to the low anhedonia group, the high anhedonia group displayed marginal differences in effort-based decision-making (EEfRT) and reduced reward sensitivity (Sweet Taste Test). Importantly, whilst there was no evidence of a difference between groups on the JORT, there was a correlation between the JORT and the EEfRT which suggests that these tasks may tap into a similar construct (motivation). The sensitivity of the EEfRT to detect changes related to anhedonia may be due to the additional cognitive decision-making component involved in this task, which is not present in the JORT.

3.4.1. Reward motivation and anhedonia

In the JORT, there was no clear evidence of a difference between the high and low anhedonia group (Figure 3.3). Both groups exerted more physical force for higher reward trials. This suggests that people with higher levels of anhedonia, at least in a non-clinical population, do not display deficits in their exertion of physical effort for reward. Using a human PRT, Hershenberg and colleagues (2016) found that people with depression displayed reduced motivation (i.e., a lower breakpoint) compared to healthy controls (Hershenberg et al., 2016). However, the PRT task used in this study required cognitive effort (not physical effort) and requires explicit decision-making (i.e., whether to accept or reject a trial). Additionally, the translational validity of the PRT has been questioned due to the rodent version failing to find a reduced breakpoint in some models of depression (chronic mild stress and maternal separation; Barr & Phillips, 1998; Shalev & Kafkafi, 2002). Nevertheless, Clery-Melin (2011) found that compared to healthy volunteers, people with depression exerted less physical force to maximize their monetary rewards on a handgrip apparatus (Cléry-Melin et al., 2011). A similar finding was found

in a button pressing task, where higher levels of anhedonia in depressed adolescents (TEPS – anticipatory score) was associated with reduced number of button presses for chocolate (Rzepa & McCabe, 2019). However, this finding was not found in a similar experiment (Rzepa et al., 2017). Whilst these studies may seem to conflict the findings presented here, it is important to note that this study included a non-clinical population, measuring anhedonia as a continuous trait, as opposed to clinical depression.

In the EEfRT, the high anhedonia group displayed a reduced proportion of hard-task choices, compared to the low anhedonia group (Figure 3.4). However, the evidence for this result was weak when an outlier was removed, and there was no evidence of a clear difference between groups on 50% probability trials, as predicted in the pre-registration. Whilst there was no robust difference between the high and low anhedonia group (based on the SHAPS) on the EEfRT, the exploratory analysis did replicate the original Treadway et al. (2009) finding that higher trait anhedonia (measured using the CPAS) was associated with reduced hard-task choices on the EEfRT (Tables 3.4 and 3.5; Treadway et al., 2009). Interestingly, both this study and the Treadway study found an association between the EEfRT and CPAS, but failed to find a robust association between the EEfRT and SHAPS (Subramaniapillai et al., 2019; Treadway et al., 2009; Yang et al., 2014). As these anhedonia questionnaires vary in a number of ways (e.g., format, temporal scale and content; see section 1.3.4), it is difficult to pin down why the EEfRT may correlate more reliably with the CPAS than the SHAPS. One possibility is that the SHAPS focuses more on consummation of reward ("I would enjoy my favourite meal") whereas the CPAS also includes questions on desire for future reward ("I have had very little desire to try new kinds of foods"), with the latter being more related to the EEfRT (although see Tran et al., 2020)(Leventhal et al., 2006; Rizvi et al., 2016). Overall, this finding highlights the value of employing multiple anhedonia questionnaires and suggests that these measures should not be used interchangeably.

There was a positive correlation between the JORT and EEfRT, which suggests that these tasks may involve overlapping behaviours related to motivation. However, only the EEfRT was related to anhedonia. A clear difference between these tasks is that the EEfRT examines decision-making (Treadway et al., 2009; similar to the rodent choice-based tasks), where a participant must weigh up the value of two alternative options, whereas the JORT (more similar to the PRT) measures physical effort exerted for a reward without explicit decision-making. Speculatively, anhedonia may not be related to reduced exertion of physical effort for reward when engaged in an activity, but rather in the explicit *choice* to engage in an effortful activity for reward (decision-making; Halahakoon et al., 2020). Further support for this may come from the finding that there was no clear evidence of a difference between groups in button pressing speed on the EEfRT. This suggests that participants were just as willing to exert effort once engaged in an effortful task. The sensitivity of the EEfRT to detect changes related to anhedonia may be due to the additional cognitive demands of this task (J. A. Cooper et al., 2019), which are not present in the JORT. In relation to the rodent literature, these findings suggest that effort-based choice tasks may provide a more sensitive measure of the motivational impairments related to anhedonia than the physical effort-for-reward tasks (such as the PRT). Nevertheless, it is important to consider alternative explanations which may account this finding such as the methodological differences between tasks (e.g., presence of probabilistic cues, reward sizes).

3.4.2. Reward sensitivity and anhedonia

In the Sweet Taste Test, the high anhedonia group displayed a reduced sensitivity to sucrose compared to the low anhedonia group (Figure 3.5). As mentioned in section 1.4.5.2, the majority of studies using this task have compared people with a clinical diagnosis (such as depression) to healthy controls, and found conflicting results (Amsterdam et al., 1987; Berlin et al., 1998; Dichter et al., 2010). In relation to anhedonia, Bedwell (2019) reported that sucrose sensitivity did not relate to anhedonia measures in a non-clinical population (Bedwell et al., 2019). One potential explanation for these conflicting results is how sucrose

sensitivity is measured. Many previous studies have measured sweet taste intensity on a point scale (i.e., rate the intensity of a given sucrose solution; Bedwell et al., 2019; Dichter et al., 2010). In contrast, this study examined detection threshold (i.e., the point at which sucrose could be detected; similar to Berlin et al., 1998). It has been suggested that point scales may not be sensitive enough to reliably detect subtle impairments in the sweet taste test (McCabe, 2018). Future studies should examine whether this effect is specific to pleasant stimuli (e.g., sucrose), or whether it could also be observed using negative stimuli (e.g., bitter tastes). This will allow us to address whether a dysfunction in sensitivity is specific to rewarding stimuli, or whether it reflects a general reduction in sensitivity. In sum, this study provides evidence that anhedonia in a non-clinical population is related to reduced reward sensitivity.

Taken together, using a battery of translational tasks designed to probe different components of reward, this study supports and extends preclinical findings by revealing that these components may also be dissociable in people. This is demonstrated by a lack of correlations between tasks: individuals who were less willing to choose the hard-task choice on the EEfRT did not display reduced sensitivity on the Sweet Taste Test. This extends preclinical finding of dissociable components of reward by observing a dissociation in humans using tasks translated from preclinical research. In this study, anhedonia was related to reduced motivation on effort-based decision-making task and reduced reward sensitivity. However, this does not seem to reflect a general reward deficit, indexed by the lack of correlation between tasks. Instead, these findings support the idea that anhedonia may be a heterogenous symptom. Specifically, there may be sub-groups of individuals who have dysfunction in different components of reward (e.g., consummatory, decisional) (Thomsen et al., 2015; Treadway & Zald, 2013). Whilst this hypothesis has been proposed before, to my knowledge it has not been directly tested. This is because most studies employ a single reward processing task alongside an anhedonia questionnaire. Further studies employing a battery of behavioural tasks (motivation, sensitivity and

learning) and self-report measures in a *clinical* population are needed to directly address this question.

3.4.3. Limitations

There was a higher proportion of males in the high anhedonia group (53%) compared to the low anhedonia group (21%), which may have influenced the differences between groups. However, including sex as an exploratory covariate in all analysis did not change the overall findings. Interestingly, few studies have investigated sex differences in anhedonia, and thus it is unknown whether the higher proportion of males in the high anhedonia group reflects a real sex difference in anhedonia (Chan et al., 2012; Yang et al., 2020) or whether this is a result of sampling.

Second, the data in the current study did not always meet the ANOVA assumptions such as normality of residuals and homogeneity of variances between groups, which could reduce the confidence in our findings. Nevertheless, ANOVA is relatively robust to slight violations to the assumption of normality provided it is not due to the presence of extreme outliers (Field, 2005).

Third, I was not blind to participant group (high or low anhedonia). This is a limitation because if an experimenter is not blind to the participant group, it can result in the observer-expectancy effect (i.e., my expectations may have unintentionally influenced the participant's behaviour). Whilst I did employ standardised instructions and procedures across all tasks to reduce biases, to eliminate the possibility of this bias would have required blinding to group (high or low anhedonia).

Fourth, it is possible that differences in behaviour on these tasks may not reflect differences in reward processing *per se.* For example, performance on these tasks could be due general impairments in perception (sweet taste test) or working memory deficits (EEfRT). Future studies would benefit from including additional controls to try to rule other potential confounds.

3.4.4. Future Directions

Based on these findings, there are benefits to employing this battery approach and therefore using a battery of translational tasks in a *clinical* population such as depression (Chapter 5) is needed. This study examined anhedonia symptoms in a non-clinical population. Whilst there are benefits of examining anhedonia a non-clinical sample (e.g., reduced likelihood of cognitive deficits, medication use and comorbidity), anhedonia levels in the clinical population are higher and may be qualitatively different.

Another area for future research is to incorporate a translational reward learning and memory task. Whilst this study focused on two main components of reward (motivation and sensitivity), another component of reward which may be compromised in anhedonia is reward learning and memory (Thomsen, 2015). Examining reward learning and memory in relation to anhedonia is important as it may help to inform recent debates on the conceptualisation and definition of anhedonia (i.e., whether there may be a sub-group of anhedonia patients with reward learning deficits; see section 1.3.2).

To conclude, this study found a dissociation between different components of reward (effort-for-reward, effort-based decision-making and reward sensitivity) using a battery of behavioural tasks (based on rodent tasks) in humans. Symptoms of anhedonia were related to reduced reward sensitivity and altered effort-based decision-making. Interestingly, as performance on the effort-based decision-making (EEfRT) and reward sensitivity (Sweet Taste Test) tasks did not correlate in this study, this could suggest heterogeneity within anhedonia (Thomsen, 2015; Treadway & Zald, 2013). Specifically, it is possible that some people with anhedonia may display impairments in their sensitivity to reward, whilst others may display impairments in decision-making to maximize reward. If this finding is also found in clinical populations, it could have important implications for the assessment and treatment of anhedonia (Treadway & Zald, 2011).

Chapter 4: Developing a translational reward learning and memory task

Chapter Aim: Develop a reward learning and memory task in a non-clinical population based on a rodent task: the reward learning assay (RLA).

Acknowledgements: Julie Lee and Sam Healer for initial support with the programming (JavaScript, CSS and HTML file).

4.1. Introduction

Depression and its symptoms are poorly understood and often resistant to available treatments (DeRubeis et al., 2005; Fava & Davidson, 1996; Trivedi et al., 2006). Despite large investments from pharmaceutical companies, the overall success rate of novel antidepressants in clinical trials remains low (Belzung, 2014; Garner, 2014). Specifically, most drugs (~90%) that appear promising in preclinical trials fail to show efficacy in clinical trials (referred to as the "translational gap"; Belzung, 2014; Garner, 2014). This is important because it has not only resulted in poor drug discovery for depression, but it has also led pharmaceutical companies to divert investments away from drug development for psychiatric conditions (Insel et al., 2013). Although several factors may contribute to this failure, a critical one is the discrepancy in how depression and its symptoms are measured in preclinical and clinical research (see section 1.4.5). To bridge this translational gap, there is a need for objective measures of symptoms of depression that can be used in *both* human and rodent research.

One promising candidate biomarker of depression, which may be particularly relevant for the symptom of anhedonia, is reward learning and memory (Halahakoon et al., 2020; Thomsen, 2015). In recent years, there has been exciting progress in translational research on reward learning using tasks such as the response bias probabilistic reward task (Der-Avakian et al., 2013; Pizzagalli et al., 2005), probabilistic reversal learning task (Bari et al., 2010; Cools et al., 2002), and the probabilistic stimulus selection task (Frank et al., 2004; see section 1.4.5.3). These have been referred to as “implicit” learning tasks because although participants are consciously aware of their choices on these tasks, they are not consciously aware of the underlying rules of the task such as the relationship between cues and their associated feedback (Frank et al., 2004). Studies using these tasks have shown that people with depression, and particularly those with higher levels of anhedonia, show deficits in reward learning.

Although these human paradigms have provided critical insights, there is a need for new reward learning and memory tasks in humans. One reason for this is that most assays have focused on "online learning", examining learning and memory over a short period of time (usually minutes; Wimmer et al., 2018). However, this contrasts preclinical tasks which often examine learning *over several days or even weeks*. This is important for translational research as it may result in different mechanisms underpinning the human and rodent tasks. Second, recent work has shown that reward learning over short time frames could, at least in part, be underpinned by working memory (Wimmer et al., 2018; Wimmer & Poldrack, 2020). This is an important potential confound in clinical studies given that many clinical populations have impairments in working memory (Christopher & MacDonald, 2005; Lee & Park, 2005; Nikolin et al., 2021; Rose & Ebmeier, 2006; Wang et al., 2017). Furthermore, most reward learning paradigms have focused on probabilistic learning. However, rewards in everyday life also vary in their value (i.e., the quality or quantity of the reward). To my knowledge, there are no translational tasks that measure learning and memory of different reward values (i.e., memory of different reward magnitudes). Based on this, there is a need for human studies to examine reward learning and memory over longer time frames and of different values of reward. This may improve translation between human and rodent work and provide a more in-depth understanding of the precise reward learning deficits in clinical populations.

Here, I focus on developing a novel human task based on a rodent reward learning and memory task: the reward learning assay (RLA; Robinson, 2018; Stuart et al., 2019). In this assay, typical rats show an intact memory for the absolute value of reward (i.e., prefering cues that have previously been associated with a high value reward than those associated with low reward values; Hinchcliffe et al., 2017; Stuart et al., 2013, 2019). However, several rodent models used to study depression (e.g., chronic pro-depressant drugs, chronic corticosterone and early-life adversity) display a blunted or reduced bias; which has been interpreted as an impaired memory for the value of reward (Stuart et al., 2019).

Given these promising findings in preclinical studies, the critical next step is to develop a human version of this task. This is necessary to examine the predictive validity of the rodent task (Robinson, 2018) and may provide an objective measure that can be used in clinical research, bridging the translational gap.

The rodent RLA takes place over five consecutive days and comprises four training days followed by a test day (see Figure 4.1). During training, rats choose between two bowls containing different digging substrates. They learn that one digging substrate is paired with reward (contains sucrose pellet/s) whereas the other substrate is paired with no reward (blank). On each day, learning is operationalized as six consecutive "correct" trials, at which point the session is terminated. Importantly, on some days (e.g., days 1 and 3) the rewarded substrate is associated with a *high reward* (2 pellets) whereas on other days (e.g., days 2 and 4) a different rewarded substrate is paired with a *low reward* (1 pellet). On the test day (day 5), rats are given a choice between the two substrates that have previously been associated with a high or low value reward. The main outcome of interest is choice bias, that is the tendency of rats to choose the substrate previously paired with a high or low reward. To ensure that the test day is examining memory for reward (and not new learning), a random reinforcement schedule (1 in 3 probability of reward) is used.

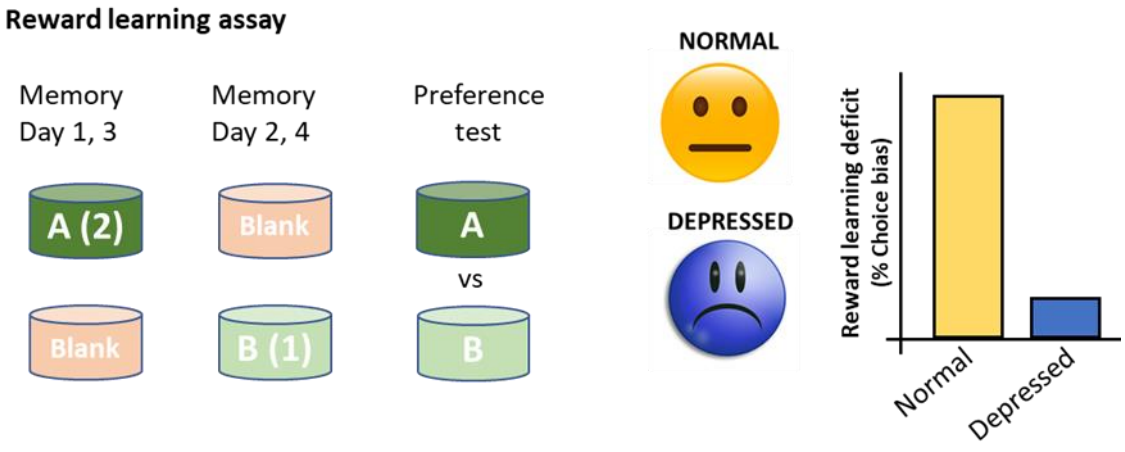

Figure 4.1. Rodent reward learning assay: digging substrates are paired with high reward (A: 2 pellets), low reward (B: 1 pellet) or no reward (Blank). On the preference test, rats are presented with substrates previously paired with a high or low reward (A versus B). Typical rats show a bias towards the high reward substrate, whereas rats subjected to models of depression show blunting of this effect.

4.1.1. Study Aim

The aim of this study was to develop a human version of the rodent RLA to enable the study of similar reward learning and memory deficits in depression. The initial task design recapitulated the main details of the rodent task and was run over five consecutive days. During the associative learning sessions (days 1 – 4), participants perform a two-alternative choice task whereby they learn to associate different stimuli (images) with a high or low reward (points exchanged for money). On the test day (day 5), participants are given a choice between images that have previously been associated with a high or low value reward. Based on the rodent task, we predicted that on the test day, participants will have a bias towards choosing the image previously associated with a high value reward. Different versions of this basic task design were piloted using an online platform (Prolific Academic) to recruit healthy volunteers.

4.2. General Methods

Ethics statement. Ethics approval was obtained from the Faculty of Life Science at the University of Bristol. All participants provided informed consent using an online consent form.

Power calculation. The studies included here are proof-of-concept studies and there was limited information that enabled the estimation of an effect size. Given that the purpose of this study was to replicate the large effect reported in the rodent task, we planned to recruit a target sample size of 35 participants to studies, which would provide us with sufficient power (.8) to detect a more conservative medium effect (Cohen's d = 0.5) at alpha = .05 for a one-sample t-test against chance performance (G*Power 3.1; Faul et al., 2007). However, due to drop-out, the achieved sample sizes varied across experiments: Experiment 1 (N = 30), Experiment 2 (N = 33) and Experiment 3 (N = 28). To try to account for drop-out in Experiment 4, we recruited more participants (N = 50) and achieved more than the target sample size (N = 37). Experiment 5 was part of a larger study and given that the effect size of interest was unclear, we recruited the maximum number of participants based on the resources we had available (N = 84 achieved sample size).

Data collection. All versions of this task were programmed in JavaScript, with the use of plugins from the jsPsych library version 5.0.1 (de Leeuw, 2015). All studies were conducted online using Prolific Academic (www.prolific.co). This platform enables participants to take part in experimental research from their own homes (Palan & Schitter, 2018; Peer et al., 2017). On Prolific Academic, participants are given a unique ID number to ensure anonymity and are then asked to complete screening questions about themselves (e.g., demographic information, mental and physical health). Researchers can then use these screening questions to recruit a specific population. Compared to traditional laboratory experiments, this online approach enables researchers to recruit more diverse populations, larger sample sizes within a short period of time and allows easier administration of longitudinal designs.

Eligibility criteria. aged 18 – 45 years, current country of residence: UK, normal or corrected-to-normal vision (i.e., reported "yes" to the question: you can see colour normally, and if you need glasses, you are wearing them or contact lenses), no diagnosed mental health condition (i.e., reported "no" to Prolific Academic screening question: "Do you have – or have you had – a diagnosed, on-going mental health/illness/condition?"), nationality: UK. Following the first experiment, subsequent studies also included a block-list (participants who had taken part in previous studies were not invited to take part in subsequent studies).

4.3. Experiment 1

4.3.1. Method

Participants. Thirty-nine participants were recruited from Prolific Academic. Four participants were excluded on Day 1 due to: fast reaction times indicating a lack of attention on the task (< 500 ms; $N = 2$), non-compliance on the task by failing to make a choice on trials ($N = 1$) and failure to meet the screening criteria (aged over 45; $N = 1$). In total, 35 participants were invited to take part in the full study. All participants were reimbursed based on the estimated time taken to complete the task at a rate of £10/hour. All participants who completed the full study also received an additional fixed bonus-payment of £5.

Design. Consistent with the rodent task, this study took place over five consecutive days: four training days (Days 1 to 4) followed by a test day (Day 5), see Figure 4.2.

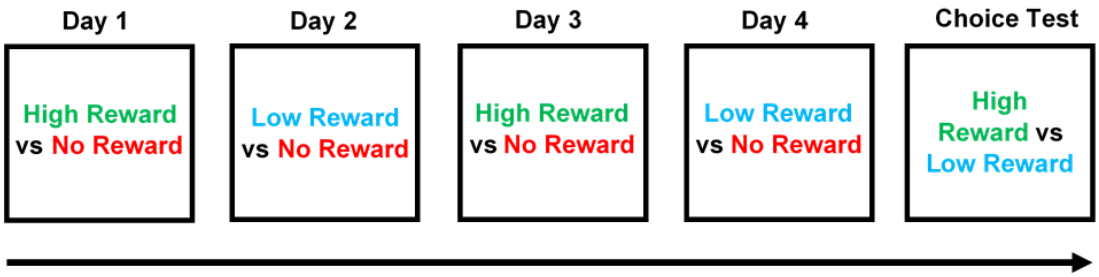

Figure 4.2. Example of the 5-day reward learning task. During training, participants learn that different images are associated with a high or low absolute value of reward. On the test day (Day 5), images previously associated with high and low reward are presented together.

Stimuli. A total of 48 images of inanimate stimuli were used, see Figure 4.3 for some example images. All images were obtained from the Bank of Standardized Stimuli (Brodeur et al., 2010), converted to greyscale and were of equal size (280 x 280 pixels). Images were then pseudo-

Figure 4.3. Example stimuli used.

randomly assigned to one of three groups: high reward (*N* = 16), low reward (*N* = 16) and no reward (*N* = 16). The high and low reward images were counterbalanced across participants.

Feedback. On high reward days, rewarded images had a higher probability of high reward: 5p (16 trials), 10p (24 trials), 50p (40 trials), £1 (48 trials). In contrast, on low reward days, rewarded images had a higher probability of low reward: 5p (48 trials), 10p (40 trials), 50p (24 trials), £1 (16 trials). This was done so that the maximum amount of money that could be won on the high reward day (£71.20) was approximately double that of the low reward day (£34.40). The sequence of the feedback was randomised (using random.shuffle in python) but the same for all participants. To encourage participants to attend to the different monetary amounts, feedback was presented in different colours: +5p (purple), + 10p (blue), + 50p (orange), + £1 (yellow), 0p (red), see Figure 4.4. At the start of the study, participants were informed that they would be paid a proportion of their total winnings (up to £5).

Reward learning and memory task

Training days. On each trial, participants are given a choice between two images: one image is associated with reward, the other is not, see Figure 4.4. Participants are asked to learn which image will win them money. They must press "S" key on the keyboard to choose the left image or "L" key to choose the right image. Participants have four seconds to make a choice, or they are timed out. Each day contains 16 pairs of images (16 rewarded images, 16 non-rewarded images). Each pair is presented eight times, resulting in 128 trials in total. Images are presented in a pseudo-random order within each block of trials (8 blocks). During training, some days provide high reward feedback (high reward days), others provide low reward feedback (low reward days). Days 1 and 3 always provide the same reward feedback and images, this is also the case for days 2 and 4. Therefore, participants learn that one set of 16 images is linked to one reward amount (day 1 and 3), whereas a different set of 16 images is linked to a different reward amount (day 2 and 4).

Similar to the rodent task, counterbalancing is done by day (whether days 1+3 or days 2+4 are the “high reward days”) and image set (which image set is associated with high or low value reward).

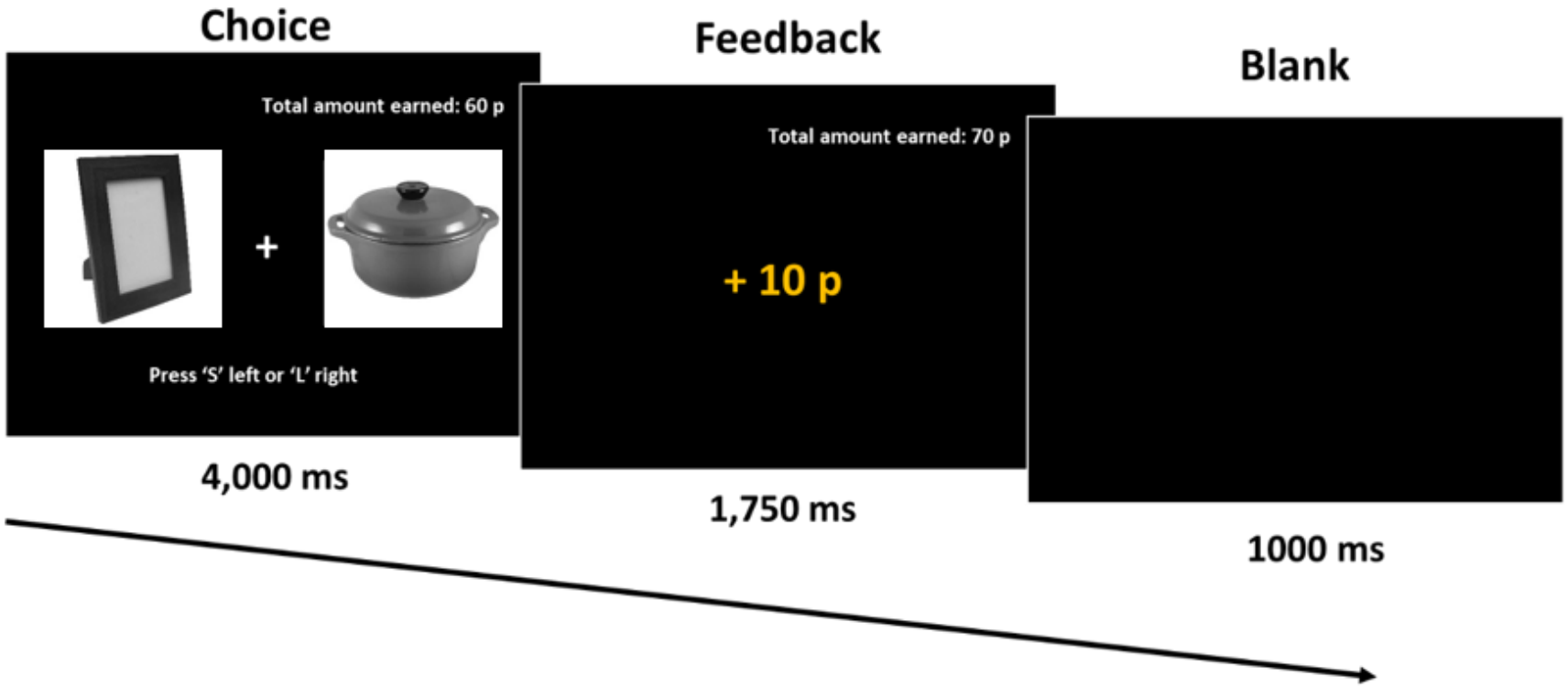

Figure 4.4. Experiment 1: Schematic of a single trial on the reward learning task (training day). Participants are given a choice between two images. Participants have to choose one of the images (one is rewarded with money, the other is not; 4 s), participants are then provided with feedback (rewarded: 5p, 10p, 50p or £1; non-rewarded: 0p; 1.75 s) followed by a blank screen (1s).

Choice test. On each trial, participants are presented with a pair of images: one image has previously been paired with higher a value reward (high reward day), the other has previously been paired with a lower value reward (low reward day). There are 16 pairs of images presented 8 times, resulting in 128 trials. The primary outcome in this task is choice bias (i.e., bias towards choosing the image previously associated with a higher value reward). This is calculated as: (the number of choices made for the high reward image / total number of trials) x 100, to provide a percentage. Consistent with the rodent task, a value of 50 is subtracted from all values. This is done so that any value above 0 indicates a positive bias (i.e., a bias towards choosing the high reward image) whereas any value below 0 indicates a negative bias (i.e., a bias towards choosing the low reward image).

Data Analysis. MATLAB and GraphPad Prism 9.0 were used to extract and visualize the data, respectively. SPSS v24 was used to conduct statistical analysis. The primary outcome of interest was bias on the choice test - whether participants display a bias towards images previously associated with high or low value reward. One-sample t-tests were conducted against no bias (0%). The secondary outcome is reaction time and learning during the training days (the percentage of correct trials on each day). This was checked to rule out the possibility that a lack of bias could be due to failure to learn during training.

4.3.2. Results and Discussion

Five participants were excluded for the following reasons: not completing all 5 days which meant that these participants did not have data on the choice test (N = 3), malfunction saving data due to a technical error (N = 1), incorrect Prolific Academic ID resulting in incorrect counterbalancing (N = 1). The final exclusion was necessary because these participants would have incorrectly been exposed to the wrong reward-image association during one of the training days. In total, 30 participants were included in the analysis (mean age = 29, 14 males).

Training days. During training, *most* participants demonstrated learning the image-reward association, indicated by the mean percentage of correct responses during training days: day 1 (*M* = 74%), day 2 (*M* = 83%), day 3 (*M* = 87%), day 4 (*M* = 89%), see Figure 4.5.

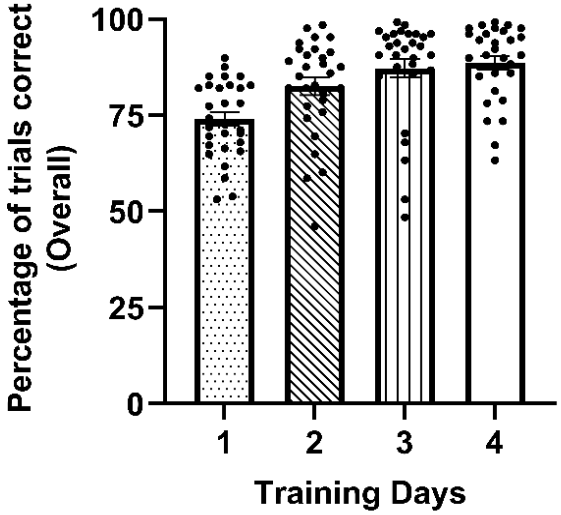

Figure 4.5. Results from training (Experiment 1): overall percentage of trials correct. Error bars represent SEM. *N* = 30.

Choice test. There was no evidence of a positive bias on the test day, $t_{(29)}$ = 1.27, *p* = .21, *M* = 3.93, 95% CI -2.39 to 10.25: participants did not show a bias towards choosing the images previously paired with a higher value reward, see Figure 4.6. To check whether this could be due to failure to learn during the training days, the analysis was re-run only including participants who scored > 70% correct on all training days. This did not qualitatively change the findings.

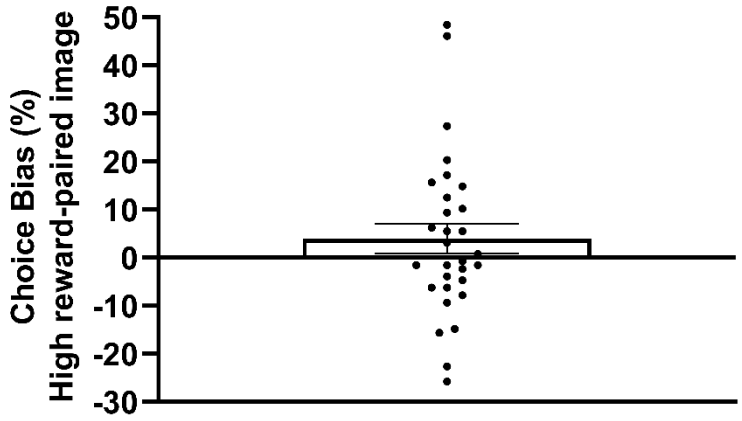

Figure 4.6. Choice bias on the test day (Experiment 1). Scores above zero indicate a positive bias (i.e., a bias towards choosing the image previously associated with the high value reward). Points represent participants. Error bars represent SEM. *N* = 30.

Overall, there was no clear evidence of a positive bias on the choice test. Given that some participants did not show strong learning of the reward-image associations during training (~ 37% did not achieve > 70% correct on all training days), the next study aimed to increase learning of the reward-image association.

4.4. Experiment 2

In Experiment 2, changes were made to encourage learning of the reward-image associations during the training days: (1) reward amounts for high and low reward days are now fixed amounts of points (i.e., no longer probabilistic), (2) there are now two sets of non-reward images (i.e., two blanks; *N* = 32 non-rewarded images) and (3) on each day, rewarded and non-rewarded images are randomly mixed during learning (previously they were presented in fixed pairs). To further motivate participants on the test day, participants were informed that only the final day counted towards their bonus-payment (up to £5).

4.4.1. Method

Participants. Forty-four participants were recruited from Prolific Academic. Based on *a priori* criteria, participants who failed to achieve > 60% accuracy on Day 1 were not invited to take part in the study (*N* = 9). Thirty-five participants were invited to take part in the full study. All participants were reimbursed based on the estimated time taken to complete the task at a rate of £10/hour. All participants who completed the full study also received an additional bonus-payment of £5.

Stimuli and Feedback. For details on the stimuli, see Experiment 1. The only difference in the stimuli used between this experiment and Experiment 1, is that this experiment included another set of non-rewarded images (*N* = 16). In Experiment 1, the same non-rewarded images were presented on all training days (*N* = 16). The simplest strategy on the previous version would therefore be to avoid the unrewarded image (*N* = 16 images), as opposed to learning which images are rewarded (*N* = 32 images). Here, two sets of unrewarded images are used to encourage participants to learn the image-reward associations during the training days. In this experiment, feedback is now fixed: high reward (+100 points), low reward (+25 points).

4.4.2. Results and Discussion

Two participants did not complete all five days and were excluded from the analysis. In total, 33 participants were included in the analysis (mean age = 29; 25 females).

Training days. During training, participants demonstrated learning, indicated by the mean percentage of correct trials: day 1 (*M* = 77%), day 2 (*M* = 80%), day 3 (*M* = 88%), day 4 (*M* = 89%), see Figure 4.7.

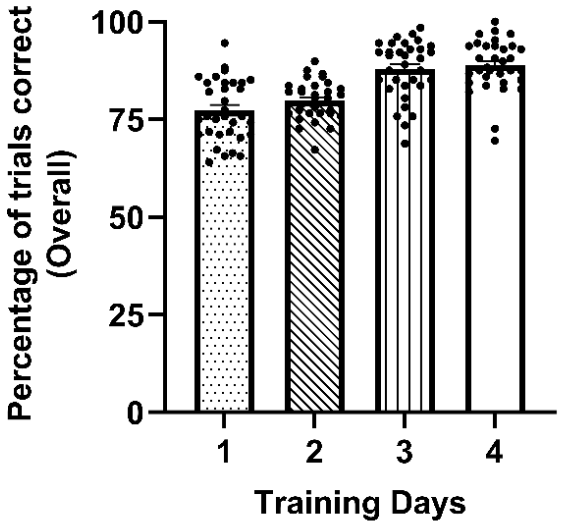

Figure 4.7. Results from training days (Experiment 2): percentage of trials correct. Error bars represent *SEM*. *N* = 33.

Choice test. There was no evidence of a bias on the choice test, $t_{(32)}$ = .63, p = .54, M = 2.15, 95% CI = -4.86 to 9.17), see Figure 4.8.

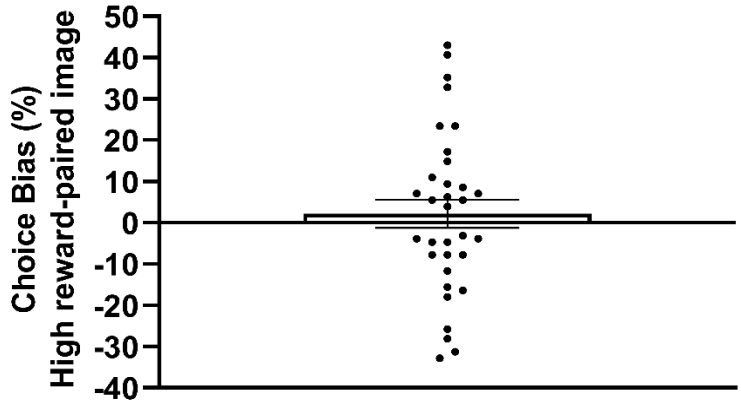

Figure 4.8. Choice bias on the test day (Experiment 2). Scores above zero indicate a positive bias (i.e., a bias towards choosing the image previously associated with high value reward). Points represent participants. Error bars represent *SEM*. *N* = 33.

Overall, whilst participants displayed learning during the training days, there was no clear evidence of a positive bias on the choice test. One possible reason for this could be the difficulty of the task (e.g., too many images to learn), which may have made it difficult for participants to recall which images are associated with high versus low points.

4.5. Experiment 3

In Experiment 3, changes were made to reduce the difficulty of the task. This involved halving the number of images (16 images in each set was reduced to 8 images in each set). This meant that there were: 8 high reward images, 8 low reward images, two sets of non-rewarded images (i.e., two blanks; *N* = 16 non-rewarded images in total). Additionally, the instructions on the final day explicitly asked participants to try to maximize their points by choosing the image associated with high reward (+ 100 points) on previous days. This makes the effect of interest an explicit memory bias, rather than an implicit bias. Given the possibility that rodents are employing an explicit memory on the RLA, the focus of this task was to assess explicit memory for higher reward images.

two sets of non-reward images (i.e., two blanks; *N* = 32 non-rewarded images)

4.5.1. Method

Participants. Fifty participants were recruited from Prolific Academic. Fifteen participants were excluded on Day 1 due to not obtaining > 60% accuracy. Thirty-five participants were invited to take part in the full study. All participants were reimbursed based on the estimated time taken to complete the task at a rate of £10/hour. All participants who completed the full study also received an additional bonus-payment of £5.

4.5.2. Results and Discussion

Seven participants did not complete the full study and were excluded from the analysis. In total, 28 participants were included in the analysis (mean age = 31; 17 female).

Training days. Participants demonstrated learning of the image-reward associations during the training sessions, indicated by the percentage of trials correct on each day: day 1 (*M* = 79%), day 2 (*M* = 81%), day 3 (*M* = 88%), day 4 (*M* = 89%), see Figure 4.9.

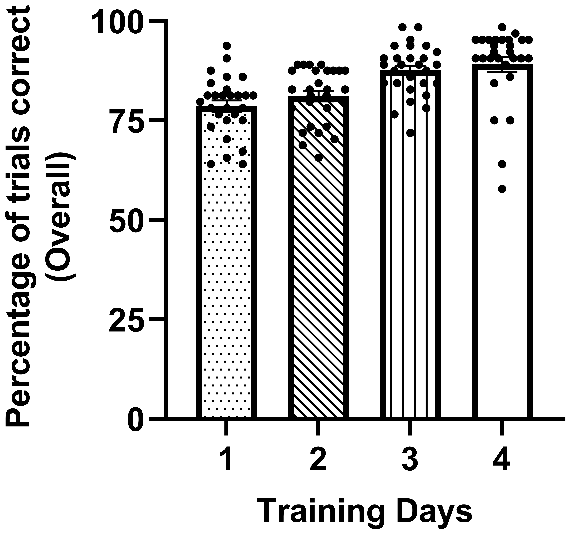

Figure 4.9. Results from training days (Experiment 3): overall percentage of trials correct. Error bars represent *SEM*. *N* = 28.

Choice test. There was weak evidence of a positive bias (*M* = 6.14, 95% CI = -.01 to 12.29) on the choice test, $t_{(27)}$ = 2.05, *p* =.050: participants exhibited a memory for the images previously associated with a higher value reward, see Figure 4.10.

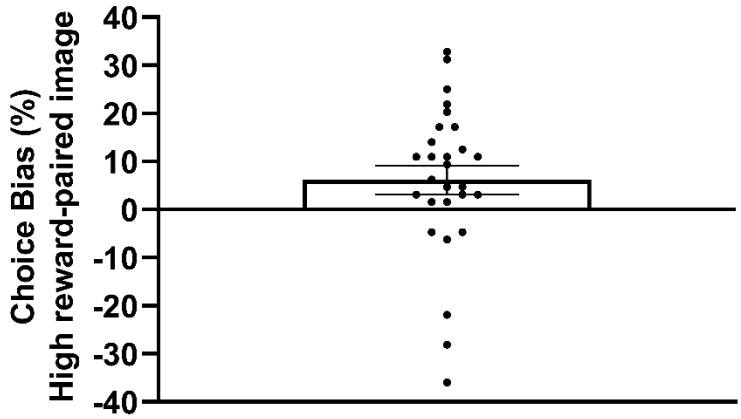

Figure 4.10. Choice bias on the test day (Experiment 3). Scores above zero indicate a positive bias (i.e., bias towards images previously associated with high value reward). Points represent participants. Error bars represent *SEM*. *N* = 28.

Overall, there was weak evidence of a positive reward-induced bias on the choice test. As we aimed to include this task in a clinical study (Chapter 5), the next experiment was designed to increase the strength of this positive bias.

4.6. Experiment 4

In Experiment 4, two changes were made to the task. First, the number of repetitions of each image was increased from 8 repetitions to 12 repetitions (96 trials in total) to enhance learning of the image-reward association in participants. Second, the final day instructions informed participants that they must choose the high reward image on *at least 60% trials* to receive the bonus payment. This was done to further motivate participants to use their memory of the value of rewards on the final day.

4.6.1. Method

Participants. Fifty-four participants were recruited from Prolific Academic. Four participants were excluded on Day 1 due to not achieving > 60% accuracy. Fifty participants were invited to take part in the full study. All participants were reimbursed based on the estimated time taken to

complete the task at a rate of £10/hour. All participants who completed the full study also received an additional bonus-payment of £5.

Data Analysis. This was similar to previous experiments, although the calculation of accuracy was adjusted: (number of trials correct image was chosen / *number of trials responded*) x 100.

4.6.2. Results and Discussion

Thirty-seven participants completed the full study (mean age = 31 years; 26 females) and were included in the analysis.

Training days. Participants demonstrated learning of the image-reward associations, indicated by the percentage of trials correct during the training days: Day 1 (M = 86%), Day 2 (M = 87%), Day 3 (93%), Day 4 (94%), see Figure 4.11.

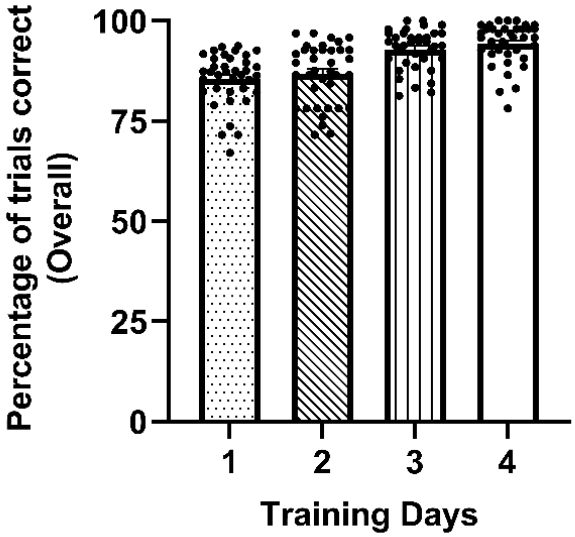

Figure 4.11. Results of training days (Experiment 4): percentage of trials correct (A) and average reaction time (ms; B). Error bars represent *SEM*. *N* = 37.

Choice Test. There was evidence of a positive bias on the choice test (*M* = 12.83, 95% CI = 5.90 to 19.77), $t_{(36)} = 3.67$, $p = .001$: participants exhibited a bias towards choosing the image previously paired with the higher value reward, see Figure 4.12.

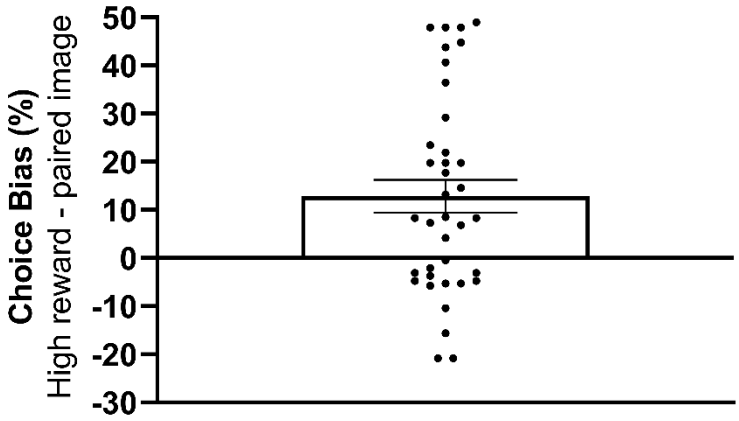

Figure 4.12. Choice bias on the test day (Experiment 4). Scores above zero indicate a positive bias (i.e., a bias towards choosing the image previously associated with high value reward). Points represent participants. Error bars represent *SEM. N* = 37.

Overall, there was evidence of a positive bias on the choice test. Whilst the mean bias is comparable to that reported in the rodent version of this task (~ 5 – 10%), the distribution of scores is not similar to the rodent task. Specifically, in the rodent task, all rats show a small but consistent positive bias. However, here there is large variability in the bias scores, with some participants achieving ceiling effects (i.e., demonstrating a strong memory of the images and their associated values). It is possible that explicitly asking participants to remember the high reward images resulted in them using different cognitive strategies to solve the task, with some participants employing higher cognitive strategies than would be used in rodents. In support of this concern, at the end of the study, participants were asked how they chose between different images on the choice test. Participants reported a range of different strategies (e.g., guessing, verbal rehearsal of images, choosing based on yesterday's images, employing a "memory map"). To try to replicate the pattern of findings similar to the RLA, a new task was developed (Experiment 5), which was designed to tap into an implicit memory bias.

4.7. Experiment 5

Given the higher cognitive strategies being used by some participants in the previous experiment, which cannot be being used by rodents, a novel task was created. This task was designed to assess a person's *implicit* memory for the value of reward ("feeling towards a better stimulus"), rather than explicit memory. To do this, we used two different cues: a primary cue (letters) which participants used during training to solve the task and a secondary cue (colours) which was present during training but was not used to solve the task. The final day, which involved random feedback, assessed whether participants would show a bias towards the secondary cue (colour) which was present on high reward days.

4.7.1. Method

Participants. One-hundred and fifty-three participants took part in the screening session (day 1). However, participants who failed to achieve the *a priori* learning criteria (75% trials correct; N = 41) or whose data did not save due to technical errors (N = 9) were not invited to take part in the full study. As this task is an implicit task, I decided to use a stricter learning criteria to ensure participants were paying adequate attention to the stimuli and task. In total, 103 participants were invited to part in the full study. All participants were reimbursed £7.50/hour for their time. All participants who completed the full study also received an additional bonus-payment (£5 based on this task).

Design. The design was the same as previous studies, there were four training days (Days 1 – 4), followed by a test day (Day 5).

Stimuli. The images used in this study were arrays of letters, see Figure 4.13 for examples. The images differed in their proportion of letters and colours. During training, there were four sets of images that contained different proportions of letters: set A (80% letter S:20% letter J), set B (20% letter S: 80% letter J), set C (80% letter C: 20% letter I) and set D (20% letter C: 80% letter I). All images contained half of the letters in the colour blue, and half of the letters in a different colour: set A and B (brown) and set C and D (purple). The test session included two sets of new images: set E (80% E: 20% T) and set F (20% E: 80% T). On all

images, half of the letters were blue, the other half of the letters were in a different colour: brown (set E) or purple (set F).

Feedback. The feedback was presented as: high reward (+100 points), low reward (+25 points) and no reward (+ 0 points). The rewarded feedback was presented in white font, the no reward feedback was presented in red font.

Reward Learning and Memory Task

Training Days. In this task, participants have to learn which images are associated with reward (points). On each trial, participants are presented with two images which vary in their proportion of letters (80:20). For example, one image would contain the letter S > J (80:20), whereas the other image would contain the opposite: J > S (80:20). Participants have to learn that one image gives them points (e.g., the image which contains the letter J > S). As in previous experiments, days with high or low reward feedback are alternated. On the high and low reward days, the letters (primary cue) and colours of the letters (secondary cue) vary. On each day, participants completed 40 trials. Counterbalancing was the same as previous experiments, by both day and image set. The aim here was to get participants to learn the task during training using a primary cue (letters), but to test if they display a bias for the secondary cue (colours) on the test day. Participants had 10 seconds to make a choice. This was followed by feedback (1.75 s) and an inter-trial interval (1 s). For example stimuli see Figure 4.13.

Choice test. On the choice test, participants are presented with novel letters (E and T). On each trial, the images differ in their proportion of each letter (E>T versus T>E) and in their colour (one image 50% brown, other image 50% purple). Similar to the rodent task, participants are provided with random reinforcement on this final day (1 in 3 probability of reward). Half of the rewarded feedback is low value reward (+25 points) and half is high value reward (+100 points). The aim of this experiment was to see whether participants would have a small bias towards choosing the *colour* (secondary cue) that has previously been associated with a high value reward (+ 100 points) during training.

Figure 4.13. Example stimuli on a low reward day (A), high reward day (B) and choice test (C). During training, participants learn to solve the task using the letters (primary cue): choosing J > S on the low reward day, and C > I on the high reward day. The arrays presented on the high and low reward days also differ in their colours (secondary cue). On the choice test, participants are presented with novel arrays of letters which differ in their letters and colour. Critically, in this example, a positive bias on the choice test would be a bias towards the image containing purple (which was presented on the high reward day). On the final day, feedback was randomly reinforced (1 in 3 probability). Note: this is an example, participants were counterbalanced by image set (whether brown or purple was the high reward) and day (whether the first day was a high or low reward day).

Data Analysis. The data is analysed similar to previous studies, except learning during the training days is not shown. This is because a high learning rate (> 75%) of the primary cue was already a requirement for inclusion in this study.

4.7.2. Results and Discussion

Eighty-four participants completed the full study (mean age = 31, 41 Female, 32% student status) and are included in the analysis.

Choice test. There was some weak evidence of a positive bias (M = 2.18, 95% CI = -.05 to 4.41), $t_{(83)}$ = 1.95, p = .055, mean bias = 2%, see Figure 4.14.

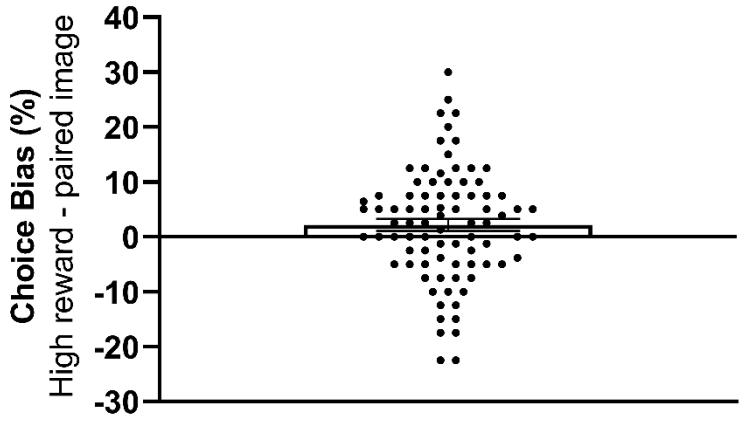

Figure 4.14. Choice bias on the test day (Experiment 5). Scores above zero indicate a positive bias (i.e., a bias towards choosing the colour previously associated with high value reward). Points represent participants. Error bars represent *SEM. N* = 84.

Overall, whilst there was weak evidence of a positive bias on this task, this effect was not robust. Nevertheless, an advantage of this version compared to previous versions is the reduced number of people achieving ceiling effects, which was an aim of this study.

4.8. General Discussion

The aim of this chapter was to develop a reward learning and memory task in humans, based on a procedurally and conceptually similar rodent task, the RLA. We run 5 versions of this task, all sharing the basic structure of the rodent RLA. The task took place over five consecutive days. During training, participants learnt that different images were associated with different values of reward (high reward, low reward, no reward). On the final day, images that were previously associated with a high or low value reward were paired together for the first time. Based on the rodent task, it was predicted that participants would display a positive bias towards the images previously associated with a high value reward, demonstrating an intact memory for the value of rewards. There was no robust evidence of a positive bias in Experiments one, two and five. However, there was evidence of a positive bias in Experiments three and four. Therefore, based on a rodent task, we provide a novel multi-day reward learning and memory task in humans.

Some experiments demonstrated evidence of a positive bias (Experiments three and four; see Figures 4.10 and 4.12), whereas others did not (Experiments one, two and five; see Figures 4.6, 4.8 and 4.14). There are several factors that differed between versions that could account for these results. One key difference is the *extent to which* the task provided explicit instructions on the choice test. The experiments that did show evidence of a bias on the choice test (Experiment three and four) explicitly asked participants to use their memory to try to choose the high reward images, making the task an explicit memory task. In contrast, the instructions in other versions (Experiment one, two and five) were less explicit and may have, to some extent, been tapping into an implicit memory bias (i.e., the participants may have not consciously recalled the images and their associated values; Squire, 2004). Another difference between versions is the task difficulty. For example, some of the experiments (Experiment one and two) were more cognitively demanding – containing a larger number of images - which could have made it too challenging to remember the image-reward associations on the choice test. Whilst there were fewer images in Experiment five, the combination

of using a secondary cue and random reinforcement on the test may have made this task too difficult. Taken together, these differences show that whilst the description of the RLA appears straightforward, the translation of this task into a human version requires careful consideration of various parameters.

Examining the face validity of this task (Experiment 3 and 4) as a human version of the RLA, the mean bias in the human task appears similar to that observed in the rodent task (see Figure 4.10 and 4.12). Specifically, participants displayed a small mean bias on the choice test (~ 5-10%), providing some face validity for this task. However, a critical difference between the human and rodent data is the distribution of the individual bias scores: there was a larger distribution of scores in the human version compared to the rodent data, with some participants achieving ceiling effects. This is an important consideration, as it may suggest that participants are using fundamentally different mechanisms to solve the task. For example, when participants were asked how they chose between images on the choice test, they reported a range of strategies, such as choosing based on yesterday's images, verbal rehearsal of the images during learning, guessing, using a "memory map". This reveals that participants were using very different strategies to solve the task, with some participants employing higher cognitive strategies. In turn, this may have resulted in high variability and ceiling effects. Therefore, whilst we have developed a novel multi-day reward learning and memory task in humans, caution should be taken at this early stage in interpreting this task as analogous to the RLA.

4.8.1. Strengths and Limitations

A key strength of this study is its translational approach, which is important for several reasons. First, it may help to bridge the gap between animal and human research (Aylward et al., 2019). Second, it may allow us to leverage one of the important strengths of preclinical research – its ability to gain insight into the *causal* neurobiological mechanisms underpinning behaviour; which is critical for the development of rationalised new antidepressants (Robinson, 2016; Treadway & Zald, 2013). Given the great promise of translational

research, there is a burgeoning need to develop cross-species behavioural assays (Barron et al., 2020; Der-Avakian & Pizzagalli, 2018; Pike et al., 2021).

Second, this task assessed learning and memory over multiple days. This is in contrast to the majority of studies used in the literature, which assess learning and memory within a single session (Wimmer et al., 2018; Wimmer & Poldrack, 2020). This is an important consideration because learning within a massed session may recruit different cognitive and neural mechanisms compared to longitudinal paradigms (see Wimmer et al., 2018). This has crucial implications for (1) translational research, as most rodent reward learning tasks are conducted over several days or weeks and (2) understanding the *precise* reward learning and memory deficits present in clinical populations (Collins et al., 2014; Wimmer & Poldrack, 2020)

Third, this study included a more diverse sample compared to most laboratory studies (Henrich et al., 2010). Psychology studies often recruit opportunity samples from within the university. A limitation of this approach is that the samples are less representative of the typical population (e.g., younger age, higher educational attainment, predominantly female), which limits the external validity of the findings (Henrich et al., 2010). In contrast, recruiting participants from online platforms such as Prolific Academic enables a more diverse demographic (geographical, socio-economic, ethnic) which is vital for improving the generalizability of the results (Peer et al., 2017).

One limitation of this task is that whilst it is procedurally similar to the RLA, there are several elements that differ between the two. For example, one difference is the presence of random reinforcement on the choice test. In the RLA, rats receive random reinforcement (1 in 3 probability of reward) on the choice test. This is done only to encourage the rats to respond and is not considered to be a critical component of the task. As humans can be asked to respond on the final day, random reinforcement was not used (in the first four versions). However, it is possible that random reinforcement on the choice test does play an

important role: speculatively, healthy rats may learn the cue-reward association during training and use this to guide behaviour in the face of misleading negative feedback on the test day. In contrast, rats with depressive-like phenotypes may learn the cue-reward associations but abandon their memory when given incorrect feedback on the test day. Therefore, depressed-like phenotype rats may have a memory for the substrates and their associated value, but may abandon this memory upon receiving negative feedback. Accordingly, the human literature has shown that people with depression are more likely to discount past reward history when given misleading negative feedback (Dombrovski et al., 2010; Murphy et al., 2003; Tavares et al., 2008). Therefore, in hindsight, it may have been advantageous to create a *procedurally* identical paradigm to increase the likelihood of translation between tasks.

A potential confound of this task is the use of language. This encompasses two aspects of the task: the stimuli (images of objects that can be verbally encoded and rehearsed) and the explicit written instructions provided to participants (Haaker et al., 2019). Both of these factors may have resulted in participants employing different, and higher, cognitive strategies to solve the task. For example, some participants reported using language to solve the task (e.g., verbal rehearsal of images during training, employing a "memory map"). To encourage translation between rodent and human studies, it may be advantageous to use stimuli that cannot be easily rehearsed (e.g., abstract images or sounds that are not easily verbalised; see Golubock & Janata, 2013) and to limit the use of verbal instructions in the task (Der-Avakian & Pizzagalli, 2018; Haaker et al., 2019).

Whilst there are advantages of conducting online behavioural experiments (e.g., diverse larger samples, efficiency), a limitation of this approach is the inability to conduct the experiment in a controlled, distraction-free environment (Palan & Schitter, 2018). Although studies have replicated findings from laboratory behavioural paradigms online (e.g., Stroop task, flanker task, attentional blink), there are concerns regarding tasks that assess cognitive-learning (see Crump et al., 2013). Consequently, it is unclear whether the failure to observe an effect in earlier experiments is

influenced by reduced attention from online participants. This could also explain the poor learning rate in Experiment 5 (which resulted in a high exclusion rate). Given the increasing number of studies being conducted online, it is critical that future studies demonstrate comparable findings in online studies using cognitive tasks typically used in the laboratory.

4.8.2. Future Directions

Future studies are needed to further develop this task as a translational assay. Based on the findings presented here, a promising approach could be to replicate this task using *identical* parameters to those used in the rodent task (Der-Avakian & Pizzagalli, 2018). The only exception to this being the modality (it may be beneficial to consider stimuli that are not easily verbalised) and reward (it is not possible to give food rewards online). To automate this task and enable flexibility in its administration (e.g., online or in the laboratory), one could employ a 3D virtual environment. Enhancing the similarity between the human and rodent tasks across all parameters may aid the translation across species (Der-Avakian & Pizzagalli, 2018; Haaker et al., 2019). In support of this approach, the use of almost identical paradigms (including virtual environments to simulate the rodent tasks) has enabled successful cross-species translation of a number of behavioural tasks (Aylward et al., 2019; Barron et al., 2020; Der-Avakian et al., 2013; Wooldridge et al., 2020).

Examining reward learning and memory in clinical populations using longitudinal paradigms may also be promising. Previous studies have proposed that patients with clinical disorders (e.g., schizophrenia, depression) or symptoms of these disorders (e.g., anhedonia) show deficits in reward learning (Frank et al., 2004; Pizzagalli et al., 2005, 2008; Waltz et al., 2007). However, more recent studies have suggested that reward learning deficits in some patient populations, such as schizophrenia, could be better explained by working memory deficits (Collins et al., 2014). To gain a better understanding of the precise reward learning and memory deficits present in patients, researchers

should also consider reward learning and memory using longitudinal paradigms (Chapter 5).

In summary, this study provides a novel multi-day reward learning and memory task in humans, and demonstrates the feasibility of running this longitudinal task on an online platform. Whilst this chapter does provide some face validity of this assay as a translational measure of the RLA, the findings do not provide convincing evidence that this version is tapping into the *same mechanism* as the rodent task. Based on this, further studies are needed to develop this assay in humans and provide evidence of its predictive validity.

Chapter 5: Depression and Reward Processing

Chapter Aim: Examine the three main components of reward processing (reward sensitivity, reward motivation and reward learning and memory) using a battery of tasks in a population of people who meet criteria for major depressive disorder.

Acknowledgements: Professor David Kessler for providing input into the recruitment and running of the study.

Note: Due to COVID-19, this study had to be stopped before reaching the pre-registered sample size. Here, I present the data collected so far as a preliminary data set. Given that the study is not powered to detect the planned effect size, inferential statistics should be interpreted with caution.

5.1. Introduction

Depression is a highly prevalent and debilitating condition. Although effective treatments do exist, there are a large proportion of patients who do not adequately respond to these treatments (DeRubeis et al., 2005; Fava & Davidson, 1996; McManus et al., 2009). One major hindrance in the development of novel rationalised treatments is our poor mechanistic understanding of depression and its symptoms, at both the behavioural and neurobiological level (Kaltenboeck & Harmer, 2018). Dysfunctional reward processing has been proposed as a promising mechanism involved in the development of depression, which may be particularly relevant for the symptom of anhedonia (Halahakoon et al., 2020; Kaltenboeck & Harmer, 2018; Nielson et al., 2020). However, the precise impairments remain elusive (section 1.4.5) as most studies do not attempt to measure different sub-components of reward processing within the same study (Nielson et al., 2020). Moreover, it is unclear whether reward processing deficits in depression are moderated or mediated by the symptom of anhedonia (measured using anhedonia questionnaires), or if they are related to other symptoms of depression (Keren et al., 2018). Gaining a clearer understanding of the relationship between depression, anhedonia and reward processing is important as it may provide a potential biomarker and treatment target for depression (Nielson et al., 2020).

Dysfunction in one or more of the following components of reward may underpin depression and its symptoms: reward motivation, reward sensitivity and/or reward learning and memory (see section 1.4.3). There has been exciting progress in the field using translational behavioural paradigms in people with depression (Berlin et al., 1998; Pizzagalli et al., 2005; Treadway et al., 2009), but there are gaps in the current literature that need to be addressed. First, few studies have examined multiple components of reward processing using a battery of tasks in the *same patient population*. This is unfortunate because it may result in erroneous conclusions being drawn (Nielson et al., 2020). For example, it is unclear whether people with depression have a generalised reward deficit (people with poorer reward motivation also have poorer reward learning and memory) or deficits in specific domains of reward processing. Employing

a battery of tasks in the same individuals instead may enable us to dissociate between reward processes and provide a more holistic understanding (Husain & Roiser, 2018; Nielson et al., 2020). Second, few studies have directly assessed anhedonia and its severity using anhedonia questionnaires (Halahakoon et al., 2020; Keren et al., 2018; McCabe, 2018; Thomsen et al., 2015). This is important because it has made it difficult to decipher whether reward deficits are specifically related to the symptom of anhedonia, or if they are related to other symptoms of depression (such as fatigue; Nielson et al., 2020)

This study extends the findings reported in Chapter 3 in two crucial ways. Firstly, it employs a battery of tasks in a *depressed population*. It is still unclear whether higher levels of anhedonia in the typical population are quantitatively (matter of degree) or qualitatively different from anhedonia in a clinical population. Thus, we aimed to assess these tasks in a depressed population to examine if the results replicate (which may suggest that anhedonia varies quantitatively along a continuum) or appear qualitatively different. Secondly, it includes a paradigm designed to assess the third main component of reward processing: reward learning and memory (Berridge et al., 2009). This is important because there is accumulating evidence that people with depression may have deficits in reward learning (Halahakoon et al., 2020; Pizzagalli et al., 2008), and it may help to inform recent debates on the conceptualisation and definition of anhedonia (i.e., whether there may be a sub-group of patients with reward learning impairments; see section 1.3.2). Therefore, this study is designed to help develop a more holistic understanding of the precise reward processing deficits in people with depression.

5.1.1. Study Aim

The aim of this study was to examine different components of reward processing using translational behavioural tasks in people with and without symptoms of depression (assessed using the Mini Neuropsychiatric Interview; M.I.N.I; Sheehan et al., 1998). Participants either did (MDD+) or did not (MDD-) meet the M.I.N.I. criteria for a Major Depressive Episode. All participants completed a battery of tasks that

assessed: reward motivation (Joystick-Operated Reward Runway Task and Effort Expenditure for Reward Task: JORT and EEfRT), reward sensitivity (Sweet Taste Test) and reward learning and memory (Reward Learning and Memory Task). All tasks are based on procedurally similar rodent tasks, see Figure 5.1. Participants also completed questionnaires that measure symptoms of depression, anhedonia, apathy and anxiety. Based on previous literature (section 1.4.5), we predicted:

H1: In the JORT, the MDD+ group will not exert more force for higher reward magnitudes, when compared to the MDD- group (i.e., there will be an interaction between reward and group).

H2: In the EEfRT, the MDD+ group will make fewer high effort/high reward choices compared to the MDD- group.

H3: In the Sweet Taste Test, the MDD+ group will have a higher detection threshold (i.e., reduced sensitivity) compared to the MDD- group.

H4: In the Reward Learning and Memory Task, the MDD+ group will show a reduced bias towards the image previously associated with a high reward, compared to the MDD- group.

Exploratory regression-based mediation and/or moderation analyses were also planned to examine whether anhedonia (measured using the SHAPS and CPAS) moderates (i.e., influences the strength or direction of a relationship) or mediates (i.e., explains why a relationship exists) any effect of Group (MDD+ or MDD-) on reward processing tasks.

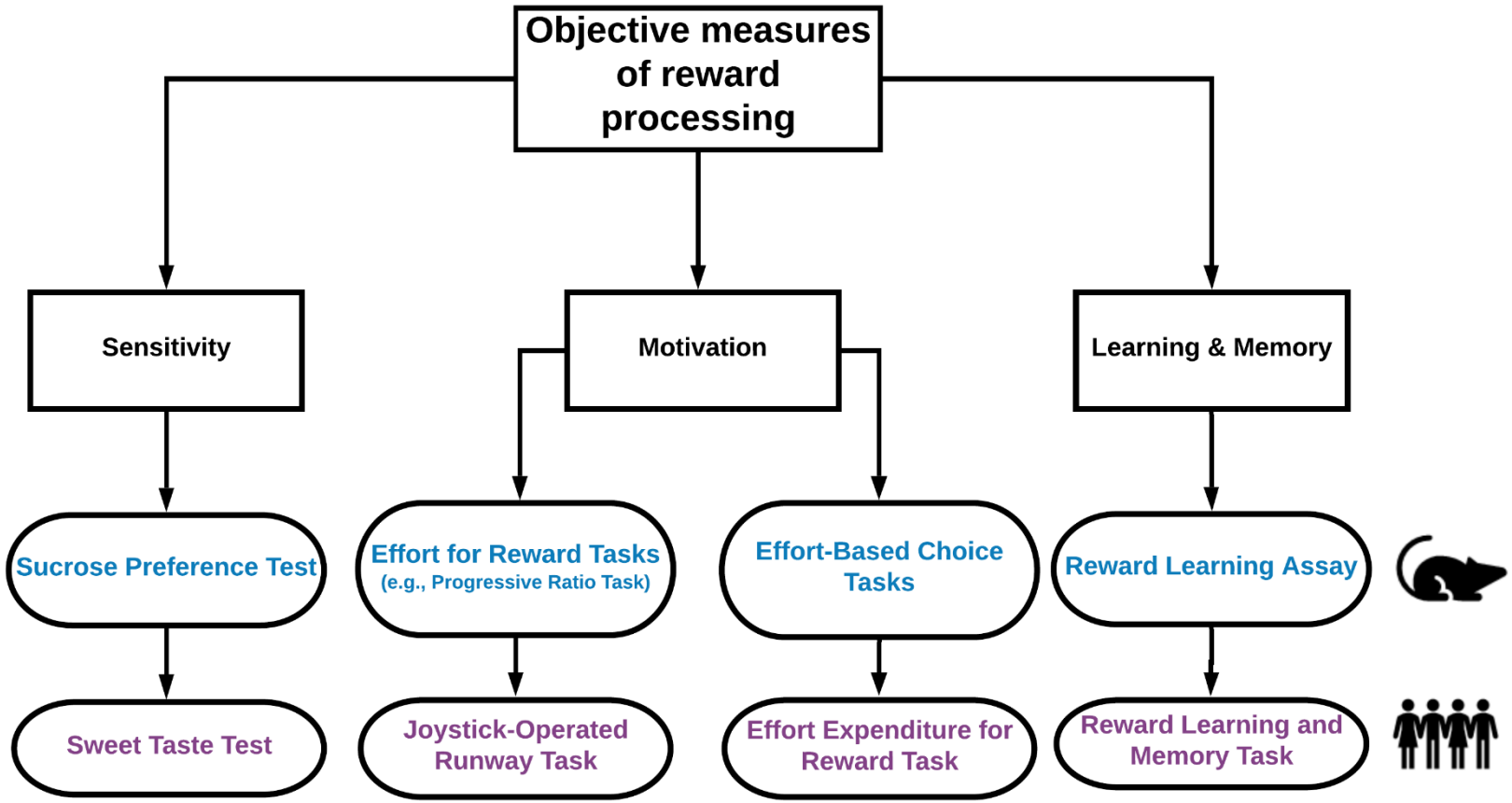

Figure 5.1. Battery of human tasks (based on rodent tasks) used in this study to measure different components of reward.

5.2. Method

The protocol was pre-registered on the Open Science Framework (OSF; https://osf.io/qrc8w/). As this is an interim analysis and data collection may be continued in the future, the protocol is currently embargoed.

5.2.1. Participants

A total of 30 participants (mean age = 25; 18 Female) were included in the study (15 MDD+, 15 MDD-). Participants were recruited using advertisements (emails via university mailing lists, posters, volunteer databases) both within the University of Bristol and in the local community. Two advertisements were created which asked for (1) people who were currently experiencing symptoms of depression or (2) people who had no current or previous psychiatric illness. Recruitment was done in blocks (e.g., recruiting ~ 10 from the MDD+ group followed by ~ 10 MDD- group).

Eligibility criteria were: aged 18 - 45 years, fluent in English, normal or corrected-to-normal vision, access to a PC (desktop or laptop), no current physical injuries, no allergy or intolerance to sugar, no disorder of taste or smell, not diabetic, not previously participated in a study using the JORT, no recreational drug use in the last 2 weeks (self-report), no change in psychotropic medication within the last 4 weeks, never taken an antipsychotic or dopaminergic medication, no first degree relative with bipolar disorder or schizophrenia.

For the MDD+ group, all participants were required to meet the M.I.N.I. criteria for a current Major Depressive Episode (MDE) and not meet criteria for severe alcohol or substance use or a psychotic episode.

For the MDD- group, participants were excluded if they met any M.I.N.I. criteria for a current or previous mental health condition (except mild or moderate alcohol or substance use) or if they had a high anhedonia score (≥ 25 on the SHAPS). This is based on a previous study (Chapter 3) showing that elevated anhedonia scores in a non-clinical population are associated with altered performance on some of the reward processing tasks included here.

Participants who completed the full study were reimbursed £60 (£40 for their time plus a £20 task-specific bonus payment). Participants who did not meet the M.I.N.I. interview criteria (and therefore did not complete the additional study visit measures) were reimbursed £30 (£20 for their time, £10 bonus payment for the online reward learning task). Whilst participants were informed that the bonus-payment was related to their performance, all participants were given the bonus-payment in full.

Ethics approval was obtained from the Faculty of Life Sciences Ethics Committee (reference: 93402) at the University of Bristol. All participants provided written informed consent.

5.2.2. Screening

This study had a two-stage screening process: (1) telephone pre-screen and (2) an in-person neuropsychiatric interview (M.I.N.I. 7.0.2 at the study visit).

During the telephone pre-screen, participants were asked questions to check their eligibility for the study. Participants who responded to the depression advertisement (MDD+ group) completed the MDE subscale on the M.I.N.I. and were invited to take part in the study if they met criteria for a current MDE. Participants who responded to the healthy volunteer advertisement (MDD- group) completed the screening questions of the MDE subscale on the M.I.N.I. and the Snaith-Hamilton Pleasure Scale (SHAPS). Participants in the MDD- group were invited to take part in the study if they had never experienced an MDE (M.I.N.I.) and did not score ≥ 25 on the SHAPS.

At the study visit, all participants completed the full screening interview (M.I.N.I.), with the exception of two modules (Suicidality and Antisocial Personality Disorder). For the MDD+ group, participants met the M.I.N.I. screening criteria if they: (1) met criteria for a current MDE and (2) did not meet criteria for psychotic features, severe alcohol use, or severe substance use. This is different to the pre-registration which had "*moderate*" alcohol or substance use and manic episode as exclusion criteria for the MDD+ group. During the study, moderate alcohol and

substance use was changed to severe. This is because the study was recruiting a predominantly student population, for which the M.I.N.I. criterion for alcohol and substance use disorder (based on the number of symptoms present in that module) was rather inclusive, and a more lenient approach was required. Due to the study's early suspension, it was also decided to analyse the data with participants who met the manic episode criteria included in the MDD+ group. This was done to increase the study's power given the small sample size.

5.2.3. Design

This study was a between-participants design. It examined differences between people who were experiencing symptoms of depression (MDD+) and those who were not (MDD-).

5.2.4. Sample Size Calculation

The intended sample size was 82 participants (41/group). An *a priori* power calculation using G*Power 3.1 (Faul et al., 2007) indicated that 82 participants provides sufficient power (.8) to detect a medium-to-large effect (Cohen's d = .62) at alpha = .05 (independent samples t-test).

This effect size was chosen based on our previous study investigating anhedonia and reward processing in a non-clinical population (Chapter 3). For the Sweet Taste Test, there was evidence of a difference between the high (M = 1.58, SD = .99) and low (M = 1.05, SD = .68) anhedonia groups (based on the SHAPS; Cohen's d = .62, N = 61). In relation to the other behavioural tasks, this sample size should enable us to detect the EEfRT effect size reported in Chapter 3 (Cohen's f = 0.27; required sample size = 74; ANOVA: Repeated measures, between factors). There was no clear evidence of a difference between groups on the JORT. However, it is possible that a difference may be observed in a clinical population based on a previous study using a physical effort for reward task (Cléry-Melin et al., 2011; Cohen'ss d = 1.21 indicating a large effect size). To my knowledge, there are no previous studies in a similar population that enable us to estimate an effect size on the reward learning and memory task.

Due to COVID-19, this study was stopped and therefore the achieved sample size (N = 30) was less than the target sample size (N = 84).

5.2.5. Behavioural Measures

Joystick-Operated Reward Runway Task

This task has been described in Chapter 3. Briefly, this is a multi-trial game whereby participants must push on a joystick to move an onscreen cursor. Trials vary in the reward on offer (0, 10, 100 or 1,000 points) and effort required to win (50, 80, 100, 120% max calibrated force). Participants must chase and catch-up with an onscreen target to win the points on offer (displayed by a cue in the top left-hand corner of the screen). This task differed from the JORT reported in Chapter 3 in two ways: the error trial was corrected for here (i.e., the trial in which no target was presented due to experimenter error now had a target) and participants were informed that they could win up to £5 based on their performance on this task alone. See chapter 3 for more details.

Effort Expenditure for Reward Task

The task is identical to that used in Chapter 3. Briefly, participants have to choose between a high effort/high reward and low effort/low reward option across many trials. Effort is exerted through button presses. Trials vary in the probability of winning money on a given trial (if they managed to complete the trial): 12%, 50% or 88%. See chapter 3 for more details. Participants were informed that they could win up to £5 based on their performance on this task.

Sweet Taste Test

This task is identical to that used in Chapter 3. Participants are given different concentrations of sucrose (0%, 0.5%, 1%, 1.5%, 2%, 2.5%, 5% w/v) in 15 mL water. On each trial, they report if they can detect the presence of sugar. A staircase method is used including five reversals. The detection threshold is the mean of the five boundaries. See chapter 3 for more details.

Reward Learning and Memory Task

This task is identical to that used in Chapter 4 (Experiment 4). Briefly, it takes place over 5 consecutive days (~ 5 - 10 minutes/day). Days one to four are training days where participants learn that different images are associated with a different value of reward (high reward, low reward, no reward). Day five is the choice test, where previously learnt high vs low reward images are paired together for the first time. Participants must try to remember and choose the images which were associated with a high reward ("+100 points"). For more details, see Experiment 4 in Chapter 3. Participants were informed that they could win up to £10 based on their performance on this task.

5.2.6. Self-report measures

All participants completed self-report measures of anhedonia: Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995), Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) and Chapman Physical Anhedonia Scale (CPAS; Chapman et al., 1976). Depression and anxiety symptoms were measured using the modified Beck Depression Inventory (BDI-II; suicidality question removed; Beck et al., 1996) and Generalised Anxiety Disorder (GAD-7; Spitzer et al., 2006), respectively. For more details, please see Chapter 2 and 3.

Generalised Anxiety Disorder-7 (GAD-7)

The GAD-7 was used to measure severity of anxiety symptoms. This is a 7-item self-report questionnaire which asks participants to report how often they have been bothered by symptoms of anxiety over the last 2 weeks. All items are rated on a 4-point scale from 0 ("not at all") to 3 ("nearly every day"). Total scores range from 0 to 21. Higher scores indicate higher symptoms of anxiety. In a heterogeneous patient sample (N = 1,201), the GAD-7 had good internal consistency (a = .88) and good convergent validity with the Beck Anxiety Inventory (r = .69; Beck & Steer, 1990; Johnson et al., 2019). It had some discriminant validity from depression measured using the BDI-II (r = .58; Johnson et al., 2019).

Other information

All participants provided demographic information (age, sex) and answered questions about: current smoking status (3 levels: yes daily, yes less than daily, not at all), income band (3 levels: low, medium, high) and financial worries (2 levels: yes or no). Participants were also asked to report if they were currently (and previously) taking any prescribed medication to treat a psychiatric or neurological condition (2 levels: yes or no). If the participant responded "yes", they were asked to report the name(s) of the medication and their time and duration of use. The questions also had the option "prefer not to say".

5.2.7. Procedure

Interested participants were sent the information sheet via email and were invited to take part in a brief telephone screen (~ 15 minutes) to further check their eligibility for the study. All participants provided verbal consent prior to completing the telephone screen. Participants who met the telephone criteria were invited to complete the online reward learning and memory task over 5 consecutive days (Monday – Friday; approximately one hour in total) followed by a single study visit.

Upon arrival at the study visit, all participants were given the information sheet, had the opportunity to ask questions and provided written informed consent before completing the M.I.N.I. screening interview (20 – 60 minutes). Following this, participants who met the criteria for the study completed the additional behavioural tasks (order: EEfRT, JORT and STT) followed by self-report measures (SHAPS, CPAS, TEPS, BDI-II, AES, GAD-7; ~ 1.5 – 2 hours). Participants who did not meet the screening interview criteria were reimbursed for their time. Upon completion, all participants were verbally debriefed and provided written final consent.

5.2.8. Data Screening

Prior to data collection, *a priori* exclusion criteria were chosen. For the questionnaire data, the AES questionnaire included an attention check question "*We would like to check that you are paying attention to your answers, so please select 'slightly true' for this question"* to ensure participants were paying attention to their responses. Any participants

who incorrectly responded to this question would have all of their questionnaire data excluded. Additionally, participants who had incomplete data (e.g., missed an answer on a questionnaire) would have their data excluded for that measure. For the Sweet Taste Test, any participants who reported detection of sugar on 0% sucrose concentrations would be excluded from the analysis for this task as an adequate detection boundary would not be possible. For the JORT, any participants who achieved over 75% trials, and therefore must have achieved one of the 120% effort trials (which were designed to be impossible), would be excluded from the JORT analysis.

5.2.9. Data Analyses

5.2.9.1. Primary Analyses

For the JORT, a 2 x 4 mixed ANOVA examined differences between groups (MDD- and MDD+) in relative average force, maximum force and reaction time. The between-subjects factor was group (2 levels: MDD+ vs MDD-). The within-subject factors were reward (4 levels: 0, 10, 100 or 1,000 points). The primary outcome was relative average force.

For the EEfRT, a 2 x 3 mixed ANOVA examined differences between groups in mean proportion of hard-task choices and reaction time. The between-subjects factor was Group (2 levels: MDD+ vs MDD-). The within-subjects factor was Probability (3 levels: 12%, 50%, 88%). The primary outcome was hard-task choices.

For the Sweet Taste Test, an independent samples t-test examined differences between groups (MDD+ and MDD-) in detection threshold.

For the Reward Learning and Memory Task, an independent samples t-test examined between groups (MDD+ and MDD-) in choice bias.

Data were extracted using Python 3.6 and MATLAB R2020a. Analyses were performed in SPSS 24 (IBM). Data were checked for normality (Kolmogorov-Smirnov), homogeneity of variances (Levene's test) and potential outliers (z-scores > 3). Where Mauchly's test of Sphericity was violated (p > .05), Greenhouse-Geisser statistics are reported. Where parametric assumptions were violated, a non-parametric test was used

where possible, or the data were transformed (only if this corrected for the assumption and did not worsen other assumptions). Data are presented with all participants retained in the analysis. Where removal of outliers substantially affects the findings, the results are also presented with the outliers excluded. Bonferroni corrections were applied to any post-hoc tests. Analyses were also re-run with exploratory potential covariates included in the models (main effects of sex, medication status and finance concerns).

5.2.9.2. Exploratory Analyses

Regression-based moderation and/or mediation analyses were planned to be conducted to examine whether anhedonia (measured using the SHAPS or CPAS) moderates or mediates any effect of group on primary outcomes. Additional correlations between performance on reward processing tasks and self-report measures were run using Spearman's correlation.

5.3. Results

For details on recruitment, see Figure 5.2. As this is an interim analysis, and further data may be collected, the data are not yet available online.

5.3.1. Demographics

In total, 15 MDD+ and 15 MDD- met the M.I.N.I. criteria. For demographic data and potential co-morbidities based on the M.I.N.I., see Table 5.1 and 5.2 respectively.

All participants were asked if they had ever received a clinical diagnosis of MDD. In the MDD+ group, 12 participants reported that they had received a diagnosis of MDD (an additional participant reported also receiving a clinical diagnosis of Borderline Personality Disorder). In the MDD- group, none of the participants had received a clinical diagnosis of MDD. Of the 15 participants in the MDD+ group, 8 were taking an antidepressant medication at the time of the study (7 SSRI alone, 1 SNRI alone; time on medication range = 2 months to 4 years). Additionally, 9 of the 15 participants in the MDD+ group met criteria for co-morbid generalised anxiety disorder as assessed by the M.I.N.I.

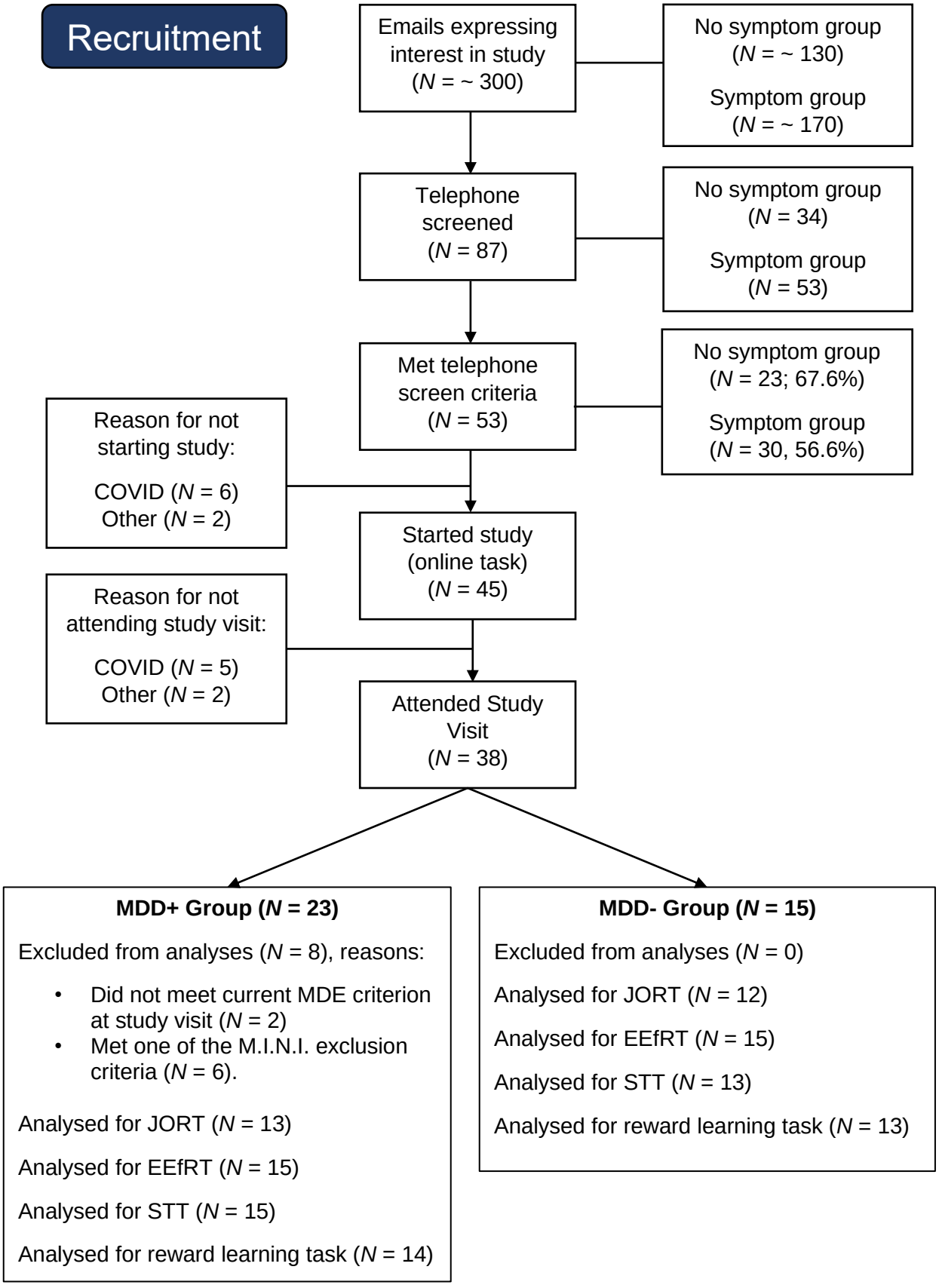

Figure 5.2. Flow diagram of study recruitment.

Abbreviations: COVID, some participants withdrew from the study or did not start the study due to concerns of COVID-19; JORT, Joystick-Operated Runway Task; EEfRT, Effort-Expenditure for Rewards Task; STT, Sweet Taste Test.

Table 5.1. Demographic data and questionnaire scores for participants in the MDD- (*N* = 15) and MDD+ group (*N* = 15).

	MDD- Group		MDD+ Group		Group Difference		
	Mean	*SD*	Mean	*SD*	*F*	*p-value*	Post-hoc
Age	25.2	6.0	25.5	7.4	.018	.89	n/a
Males (*N*)	5	33%	7	47%	X^2=.56	.46	n/a
Smoking Status	2.7	0.5	2.6	0.6	X^2=1.05	.59	n/a
Income	2.4	0.7	2.3	0.6	X^2=1.31	.52	n/a
Money Concern	1.2	0.4	1.7	0.5	X^2=6.65	.01	MDD+ > MDD-
SHAPS	17.3	2.9	31.9	6.1	68.84	<.001	MDD+ > MDD-
SHAPS – D	0	0	5.1	3.0	44.01	<.001	MDD+ > MDD-
CPAS	10.5	6.1	21.5	8.9	15.69	<.001	MDD+ > MDD-
TEPS – A	47.3	7.7	32.7	6.1	33.15	<.001	MDD+ < MDD-
TEPS – C	38.8	5.8	26.9	7.6	23.07	<.001	MDD+ < MDD-
BDI-II	3.5	2.8	31.1	8.1	154.19	<.001	MDD+ > MDD-
Apathy Scale	23.9	5.2	41.9	8.52	48.63	<.001	MDD+ > MDD-
GAD-7	1.7	1.1	12.8	3.3	151.88	<.001	MDD+ > MDD-

Abbreviations: smoking status (1=yes daily, 2= yes less than daily, 3=never); income (1=high, 2=medium, 3=low); money concern (1=no, 2=yes); SHAPS, Snaith Hamilton Pleasure Scale; TEPS, Temporal Experience of Pleasure Scale (A, anticipatory; C, consummatory); BDI-II, Beck Depression Inventory; GAD-7; Generalised Anxiety Disorder-7; n/a, not applicable. Welch's ANOVA and Chi Square run to compare groups. MDD+ (*N* = 15), MDD- (*N* = 15).

Table 5.2. M.I.N.I. subscale criterion met for each group.

M.I.N.I. criteria	MDD+ Group	MDD- Group
Major Depressive Episode (MDE)	15	0
MDE – Anhedonia Question	14	0
Mania (manic episode, hypomanic episode, or hypomanic symptoms)	4	0
Panic disorder	current = 3 lifetime = 3	0
Agoraphobia	3	0
Social Anxiety Disorder	5	0
OCD	5	0
PTSD	3	0
Alcohol use	mild = 4 moderate = 2	mild = 1
Substance use	mild = 3	mild = 1
Psychotic features	0	0
Anorexia	0	0
Bulimia	2	0
Binge eating disorder	0	0
Generalised Anxiety Disorder	9	0
Antidepressant use	8	0

Abbreviations: MDE, Major Depressive Episode (all MDD+ participants met criteria for a current MDE, none of the MDD- group met criteria for current or past MDE); MDE – Anhedonia Question, responded "yes" to the anhedonia question on the MDE subscale of the M.I.N.I; OCD, Obsessive Compulsive Disorder; PTSD, Post Traumatic Stress Disorder; Antidepressant use, currently taking antidepressants.

5.3.2. Primary Analyses

5.3.2.1. Joystick-Operated Reward Runway Task

Five participants achieved over 75% of trials and were excluded from the analysis: 25 participants (MDD+ = 13, MDD- = 12) were included in the analysis.

Data Assumptions. For reaction time, homogeneity of variances (*p*s < .052) was violated (*p*s < .052) and 0-point trials did not meet normality (*p* = .069). Log transformations improved the assumption of normality

but worsened homogeneity of variances, and so analysis is done on non-transformed data.

Average force. There was evidence of a main effect of reward, $F_{(1.15,26.49)}$ = 25.32, p <.001, n_p^2 = .52. Participants exerted more force for higher reward magnitudes: 0 points (M = 50.19, SE = 3.11), 10 points (M = 57.26, SE = 2.21), 100 points (M = 61.01, SE = 1.96) and 1,000 points (M = 64.37, SE = 1.85). Bonferroni-corrected pairwise comparisons revealed differences across all reward magnitudes (ps ≤ .006). There was no evidence of a main effect of group ($F_{(1,23)}$ = 1.48, p = .24, n_p^2 = .06; see Figure 5.3) or reward x group interaction ($F_{(1.15,26.49)}$ = 0.67, p = .44, n_p^2 = .028). Re-running the analysis with potential covariates revealed evidence of a main effect of sex, *(*p = .003), sex x reward interaction, *(*p = .021), and reward x finance concern interaction (p = .025). Including these covariates did not qualitatively change the findings.

Maximum force. There was evidence of a main effect of reward, $F_{(1.22, 28.08)}$ = 28.49, p < .001, n_p^2= .55. Participants exerted more force for higher reward magnitudes: 0 points (M = 72.77, SE = 4.70), 10 points (M = 83.90, SE = 3.59), 100 points (M = 89.70, SE = 3.23) and 1,000 points (M = 93.93, SE = 3.19). Bonferroni-corrected pairwise comparisons revealed differences across all reward magnitudes (ps ≤ .003). There was no evidence of a main effect of group ($F_{(1, 23)}$ = .09, p = .77, n_p^2 = .004; see Figure 5.3) or reward x group interaction ($F_{(1.22, 28.08)}$ = 1.71, p = .20, n_p^2 = .07). Re-running the analysis including the potential covariates: there was evidence of a main effect of sex (p = .031), reward x sex interaction (p = .011) and reward x finance concern interaction (p = .022). Including these covariates did not qualitatively change the findings.

Reaction time. There was evidence of a main effect of reward, $F_{(3, 69)}$ = 9.19, p < .001, n_p^2 = .29. Participants were quicker to respond on higher reward trials: 0 points (M = 518, SE = 18), 10 points (M = 487, SE = 14), 100 points (M = 486, SE = 16) and 1,000 points (M = 477, SE = 16). Bonferroni-corrected pairwise comparisons revealed slower reaction times on 0-point trials compared to all other reward magnitudes (ps ≤

.019). There was no evidence of a difference between other reward magnitudes in reaction time (*p*s = 1.0). There was no evidence of a main effect of group ($F_{(1,23)}$ = 2.56, p = .12, n_p^2 = .10; see Figure 5.3) or reward x group interaction ($F_{(3,69)}$ = .13, p = .94, n_p^2 = .006).

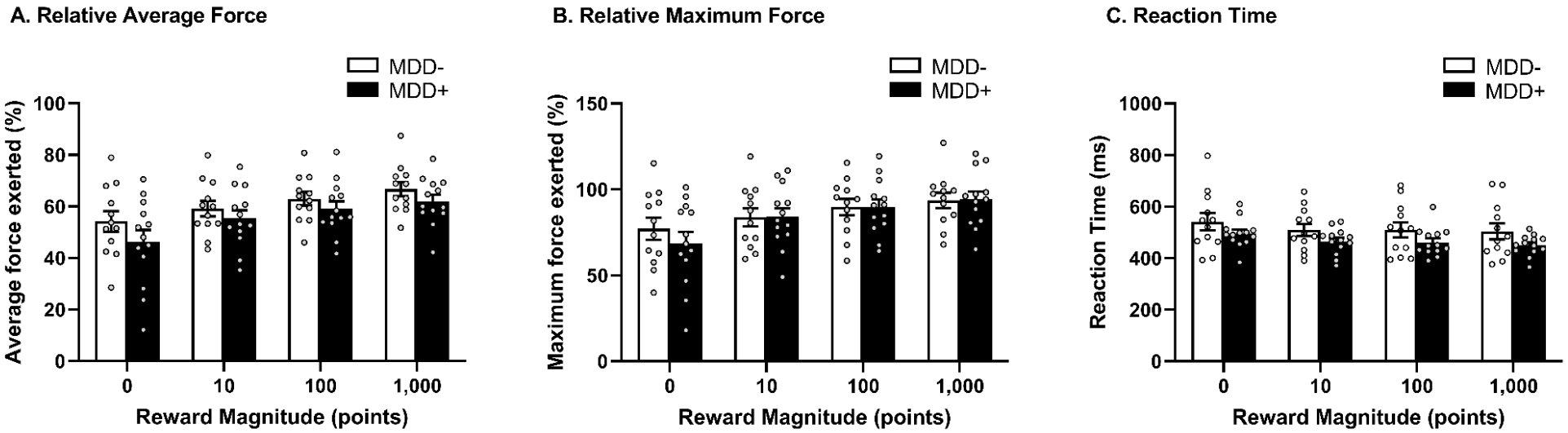

Figure 5.3. Differences between the MDD- and MDD+ group on the JORT: relative average force (A) maximum force (B) and reaction time (C; ms). Bars represent Mean and *SEM*. Points represent participants. *N* = 12 MDD-, 13 MDD+.

5.3.2.2. Effort Expenditure for Reward Task

Consistent with Treadway (2009), only the first 50 trials were used. Trials in which the participant did not make a choice within the time limit were not included in the analysis (M = 49.9, SD = 0.3, range = 49 to 50).

Data assumptions. For proportion of hard-task choices, there was evidence of non-normality for all trial types except medium and high probability trials for the MDD+ group (ps ≤ .037). For reaction time, there was evidence of non-normality for low and high probability trials for the MDD+ group (ps ≤.029). Transformations did not improve normality and so analysis was done on non-transformed data.

Proportion of hard task choices. There was evidence of a main effect of probability, $F_{(2,56)}$ = 83.55, p <.001, n_p^2 = .75. Participants chose the hard-task choice more often when the probability was higher: 12% (M = 11.57, SE = 2.95), 50% (M = 45.83, SE = 3.68), 88% (M = 67.19, SE = 3.01). Bonferroni-corrected pairwise comparisons revealed differences across all probabilities (ps < .001). There was no evidence of a main effect of group, $F_{(1,28)}$ = .73, p = .40, n_p^2 = .03, or group x probability interaction, $F_{(2,56)}$ = 1.83, p = .17, n_p^2 = .06, see Figure 5.4.

Reaction time. There was evidence of a main effect of probability, $F_{(1.63,45.64)}$ = 6.35, p = .006, n_p^2 =.19. Bonferroni-corrected pairwise comparisons revealed participants were quicker on 12% trials (M = 1.50, SE = 0.74) compared to 50% trials (M = 1.70, SE = .09; p =.004); and quicker on 88% trials (M = 1.59, SE = .07) compared to 50% trials (p = .051). There was no evidence of a difference between reaction time on 12% and 88% trials (p = .54). There was no evidence of a main effect of group ($F_{(1,28)}$ = .78, p = .39, n_p^2 =.03) or a probability x group interaction ($F_{(1.63,45.64)}$ = .15, p = .82, n_p^2 =.005), see Figure 5.4.

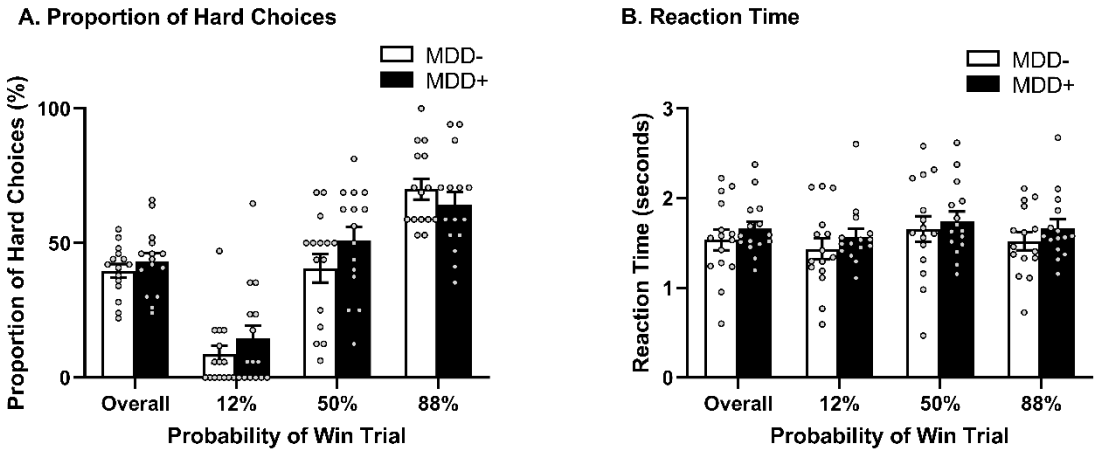

Figure 5.4. Differences between the MDD- and MDD+ group on the EEfRT across different probability levels: (A) mean proportion of hard-task choices and (B) reaction time (seconds). Bars represent mean and *SEM*. Points represent participants. *N* = 15 MDD-, 15 MDD+.

Finger tapping speed. There was no evidence of a difference between the MDD- and MDD+ in finger tapping speed prior to the task, $t_{(24.09)}$ = .34, *p* = .73. Additionally, there was no evidence of a difference between groups in mean button pressing rate (i.e., button pressing speed) for the easy or hard-task choices (*p*s ≥ .73).

Trials completed. The mean number of trials completed was 98.2% (*SD* = 4.80, range = 76 – 100%). There were no participants that only chose the easy or hard task. There was weak evidence that the MDD+ group completed fewer trials (*M* = 96.7, *SD* = 6.4) than the MDD- group (*M* = 99.73, *SD* = 1.03, *p* = .089).

5.3.2.3. Sweet Taste Test

One participant was excluded due to reporting sucrose in 0% sucrose concentrations and another participant was excluded as only four boundaries were available due to experimenter error. In total, 28 participants (MDD+ = 15, MDD- = 13) were included in the analysis.

There was no evidence of a difference between groups on mean detection threshold, $t_{(26)}$ = .36, *p* = .73, see Figure 5.5. As the data did not meet

the assumption of normality, analysis was re-run using a Mann Whitney *U* test: this did not qualitatively change the findings (p = .56). Re-running the analysis with potential covariates included, there was weak evidence of a main effect of medication use, $F_{(1, 23)}$ = 3.31, p = .082, n_p^2 = .13; N = 8): people taking medication had higher detection thresholds (i.e., poorer detection; M = 1.93, SE = .41; N = 8) than people not taking medication (M = 1.00, SE = .24; N = 20).

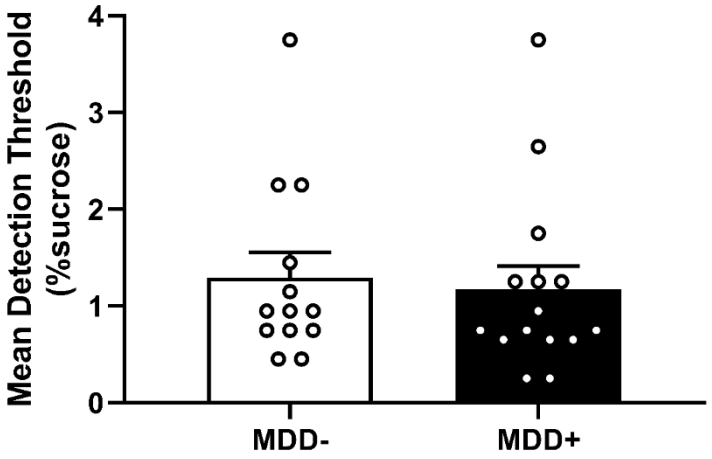

Figure 5.5. Difference between the MDD- and MDD+ group in the Sweet Taste Test. Bars represent mean and SEM. Points represent participants. N = 13 MDD-, 15 MDD+.

5.3.2.4. Reward Learning and Memory Task

Three participants did not complete all five days of the task, resulting in 27 participants (14 MDD+, 13 MDD-) being included in the analysis.

Choice Test. There was evidence of an overall positive bias, $t_{(26)}$ = 2.76, p = .011, mean bias = 12.47), demonstrating learning and memory for the high reward images. There was no evidence of a difference between groups, $t_{(25)}$ = .13, p = .90, see Figure 5.6. Re-running the analysis with potential covariates, there was evidence of a main effect of finance concerns (p = .033): participants who reported "yes" to finance concerns had higher bias scores (M = 23% bias, SE = 8; N = 12) than individuals who reported "no" (M = -1% bias, SE = 8; N = 15).

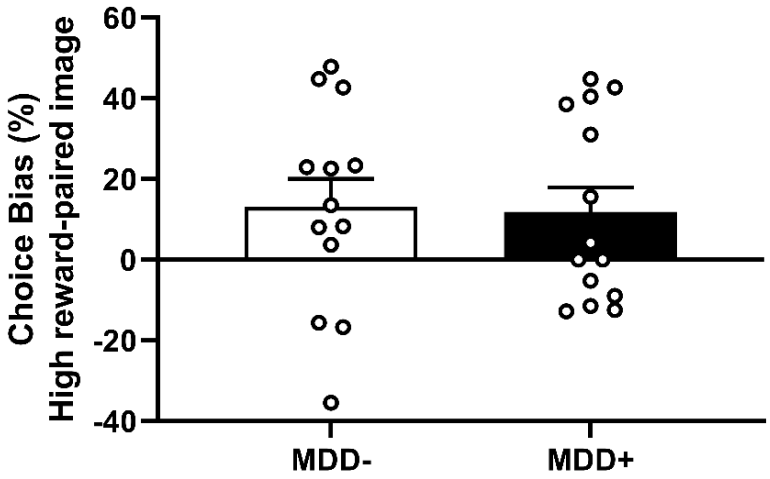

Figure 5.6. Difference between the MDD- and MDD+ group in the reward learning and memory task – choice test. Bars represent mean and *SEM*. Points represent iparticipants. *N* = 13 MDD-, 15 MDD+.

5.3.3. Exploratory Analyses

5.3.3.1. Correlations between tasks and self-report measures.

Correlations were explored for each group separately. In the EEfRT, there was evidence of a positive correlation between anxiety (GAD-7) and proportion of hard-task choices (r = .76, p = .001), suggesting people with higher levels of anxiety chose the hard-task choice more often in the MDD+ group. In the Sweet Taste Test, there was weak evidence of a positive correlation between mean detection threshold and symptoms of depression (BDI-II; r = .49, p = .065) and anhedonia (SHAPS_D; r = .50, p = .058) in the MDD+ group. In the reward learning and memory task, there was a positive correlation between choice bias and symptoms of depression (BDI-II; r = .59, p = .025) and anhedonia (SHAPS; r = .59, p = .027) and weak evidence of a negative correlation with anxiety (GAD-7, r = -.47, p = .09). There was no clear evidence of any other correlations, ps ≥ .10). Given the small sample size and that these correlations were not corrected for multiple comparisons (due to them being exploratory), these results should be considered as hypothesis-generating, not confirmatory.

5.3.3.2. Correlations between tasks.

There was no evidence of a correlation between tasks (*p*s ≥ .16).

5.4. Discussion

This study supports and extends previous findings showing that different components of reward may be dissociable in people (Chapter 3), indicated by the lack of correlations between tasks. In relation to depression, there was no clear evidence of a difference between the groups (MDD+ vs MDD-) on any of the reward processing paradigms. As this study did not recruit to the pre-determined sample size, we must be cautious in the interpretation of these findings. Nevertheless, I will briefly discuss these findings in relation to current literature before discussing possible future directions of this work. Given the exciting potential of reward processing as a biomarker and therapeutic target for depression (Nielson et al., 2020), it is crucial that we gain a clearer understanding of this relationship.

5.4.1. Reward motivation

In the JORT, there was no clear evidence of a difference between the MDD+ and MDD- group (Figure 5.3), both groups exerted more physical force for higher reward trials. To my knowledge, only one study has previously examined physical effort exerted for reward in depression using a similar task (Cléry-Melin et al., 2011). Clery-Melin et al. (2011) found that, in contrast to healthy controls, patients with depression did not exert more physical force on a handgrip apparatus for high compared to low reward trials (i.e., they showed a blunted response), suggesting that people with depression have dysfunctional incentive motivation. However, the preliminary results of the present study do not support this finding. It is important to note that we included a predominantly student population, whereas Clery-Melin et al. (2011) included a hospitalised population. Speculatively, it is possible that reduced incentive motivation may be related to general functioning, and may not be as apparent in a high functioning population (despite experiencing symptoms of depression). Overall, given the sparsity of studies examining physical

effort for reward in depression (Halahakoon et al., 2020), additional work is required to clarify whether reward motivation can be dissociated in depressed vs healthy controls in a non-hospitalised population.

In the EEfRT, there was no clear evidence of a difference between the MDD+ and MDD- group (Figure 5.4). This contrasts with previous studies which have reported fewer hard-task choices in people with depression compared to healthy controls (Treadway et al., 2012; Yang et al., 2014), suggesting that depression is characterised by impaired effort-based decision-making to maximize rewards. One notable difference between the current study and previous clinical studies is the proportion of hard-task choices in the healthy control group: in this study, the healthy control group had a lower proportion of hard-task choices (40%) compared to previous studies (~ 55 - 61%; Barch et al., 2014; Treadway et al., 2012; Yang et al., 2014). This is important because the mean proportion of hard-task choices in our MDD+ group is consistent with the original Treadway et al. (2012) study (both 43%), suggesting that differences in the control groups could, in part, contribute to the discrepancy between studies (Treadway et al., 2012). The reason for this difference is unclear, but the mean proportion of hard-task choices in the present study are comparable to our previous study in a non-clinical population (Chapter 3) and other studies (37% in a community sample in Addicott et al., 2020). Therefore, performance in the healthy control group is an important consideration for future studies using this task.

5.4.2. Reward sensitivity

In the Sweet Taste Test, there was no clear evidence of a difference between the MDD+ and the MDD- group (Figure 5.5). This supports the findings reported by Dichter et al. (2010), who found no clear evidence of a difference between depressed and non-depressed participants in sensitivity to sucrose (Dichter et al., 2010), but it contrasts with other studies that found poorer sucrose sensitivity in people with depression compared to healthy controls (Amsterdam et al., 1987; Berlin et al., 1998). However, it should be noted that we did find weak evidence of a positive correlation between detection threshold and symptoms of

depression (BDI-II) and anhedonia (SHAPS) in the predicted direction (i.e., people with higher symptoms had poorer detection of sucrose). Moreover, as pointed out by Dichter et al. (2010), caution should be taken in the interpretation of their findings given the small sample size (*N* = 30) and small-to-medium effect sizes (Cohen's *D* = 0.37 to 0.51; Dichter et al., 2010). Thus, whilst there does not appear to be a robust difference between the groups on the sweet taste test, larger studies are needed to further interrogate this finding.

5.4.3. Reward learning and memory

In the reward learning and memory task, there was no clear evidence of a difference between groups (MDD+ and MDD-; Figure 5.6). Whilst this may appear to disagree with previous studies reporting reward learning deficits in people with depression (Halahakoon et al., 2020), a possible difference between the present paradigm and other tasks used in the literature is the extent to which they measure implicit versus explicit learning and memory: our study explicitly asks participants to try to recall the high-value reward images (in exchange for money) making this an explicit memory task. Conversely, many of the reward learning tasks used in the depression literature are designed to assess implicit learning about a cue-reward relationship (Frank et al., 2004; Pizzagalli et al., 2005). Therefore, we found no evidence of an explicit reward memory deficit in people with depression, when compared to healthy controls.

Taken together, we did not find any clear evidence that people with symptoms of depression differ from those without symptoms of depression on a battery of reward processing tasks. However, it is important to note that this interim analysis includes a small sample size which increases the likelihood that there are Type II errors (i.e., stating that this is no effect when there is a true effect) and Type I errors (i.e., stating that there is an effect when there is no true effect)(Button et al., 2013). Given the important link between depression and reward processing, there is a clear need to continue this work to the pre-registered sample size. This will also be necessary to further interrogate

the potential moderating or mediating effect of anhedonia on this relationship.

5.4.4. Limitations

One limitation of this study is that it was not conducted to its planned sample size (N = 84), which makes interpretation of null results problematic. Specifically, it is likely that we would only be able to detect very large effects between groups and cannot refute the possibility of smaller effects (which may be expected).

Secondly, many MDD+ participants were taking an antidepressant medication (7/15; mostly SSRIs). Due to the well-documented difficulty of recruiting participants in depression research (Hughes-Morley et al., 2015), we decided not to have antidepressant use as an additional exclusion criteria. However, SSRIs may affect performance on behavioural tasks (Godlewska et al., 2016; Harmer et al., 2009), and could have masked potential differences between groups. Although this is a crucial consideration, it is important to note that: (1) previous studies using similar tasks (EEfRT, handgrip task, sweet taste test) have reported that people with depression show deficits on these tasks despite taking an SSRI medication (Berlin et al., 1998; Cléry-Melin et al., 2011; Treadway et al., 2012); (2) all participants in this study had been taking their medication for a period of at least 2 months, so it is likely that these participants had not adequately responded to their medication; (3) theoretically, if reward processing tasks are related to anhedonia, we may predict that SSRIs would not improve performance given that serotonergic antidepressants are not very effective in the treatment of anhedonia (Nutt et al., 2007).

Thirdly, most participants were recruited from within the university, which limits the generalisability of these findings to the broader population. Whilst the aim of this study was to initially advertise within the university, and then to advertise within the local community (online Bristol newspapers, support groups), there was a larger response rate (~ 300 emails within 2 - 3 months) to the university advertisements than

anticipated. Consequently, advertisements outside the university were not yet widely distributed. Further continuation of this study should focus recruitment efforts outside the university to enhance the ecological validity of the findings.

5.4.5. Future Directions

There is a need for studies to employ a battery of tasks in a *larger* population of people who meet criteria for anhedonia. Specifically, it may be useful to investigate anhedonia across different clinical populations (Lambert et al., 2018; Thomsen et al., 2015). Whilst we focus on depression in this study, it is possible that anhedonia reported in other clinical disorders (e.g., schizophrenia, PTSD) is qualitatively different. Examining anhedonia across disorders is in line with the RDoC (Insel et al., 2010), and may enable further insight into the multifaceted nature of this condition.

Another area for future research is to triangulate across different methods. For example, this study focuses on dissociating components of reward using translational behavioural tasks. One clear advantage of this approach is that it promotes cross-species research (Thomsen et al., 2015). However, there are other methods that may also help to improve our understanding of the reward processing abnormalities in depression and anhedonia, such as neuroimaging and computational modelling (Robinson & Chase, 2017; Rzepa et al., 2017). For example, given the excellent temporal resolution of electroencephalography (EEG), future studies could try to investigate the temporal signature of different reward components within a trial (Chen et al., 2018; Glazer et al., 2018; Keren et al., 2018). On the other hand, computational psychiatry may enable us to tease apart multiple parameters (e.g., learning, sensitivity) within a single task, providing more specific insights into the underlying deficits (Huys et al., 2013; Robinson & Chase, 2017). This is important because whilst we have tried to dissociate these components using different behavioural tasks, it is often difficult to rule out the involvement of other processes. For example, on a reward motivation task a patient may exert

less effort for reward because they are less sensitive to the reward, more sensitive to the effort or both (Bonnelle et al., 2015). Computational modelling is well suited to addressing this question (Pessiglione et al., 2018). Triangulating across these different methods may enable more robust conclusions to be drawn about the relationship between depression and reward processing.

To conclude, using a battery of translational reward processing tasks in people with depression, this preliminary study found further evidence that different components of reward (effort-for-reward, effort-based decision-making, reward sensitivity, reward learning and memory) may be dissociable in people, replicating the findings of Chapter 3. However, there was no clear evidence that depression affected performance on any of these reward processing tasks. As this is an interim analysis, replication of these results in a larger sample is required.

Chapter 6:
General Discussion

6.1. Thesis aims

The overarching aim of this thesis was to develop a more complete understanding of the reward processing deficits related to anhedonia. Specifically, it aimed to address three gaps within the literature: (1) the lack of objective measures of components of reward (particularly, tasks that could be applied in both humans and rodents); (2) the lack of studies measuring multiple components of reward in the same population of people; (3) the lack of studies directly assessing anhedonia and its severity using anhedonia questionnaires (instead most studies examine clinical populations without directly measuring anhedonia).

Here, I contribute to the first gap by developing two simple behavioural tasks designed to measure reward motivation (JORT; Chapter 2) and reward learning and memory (Chapter 4). I address the second and third gaps by examining multiple domains of reward alongside anhedonia questionnaires in a non-clinical population with higher levels of anhedonia (Chapter 3) and in a depressed population (Chapter 5). In this Chapter, I will provide a brief overview of these methods and findings, discuss the implications and limitations of this work, and suggest possible future directions.

6.2. Overview of findings

6.2.1. Development of reward processing tasks

There are few behavioural tasks that measure specific domains of reward processing in humans (section 1.4.5). Given that preclinical studies have provided compelling evidence demonstrating that reward processing can be fractionated into at least three dissociable sub-components (motivation, consummation, learning; Berridge & Robinson, 2003), this is a key limitation in the human literature. Consequently, and in line with one of the key objectives of the RDoC (Insel et al., 2010), there is a need for behavioural tasks that measure "purer" psychological constructs. This thesis contributes to this endeavour, by providing proof-of-concept for two behavioural tasks designed to measure reward motivation (effort-expenditure for reward) and reward learning and memory (based on a

rodent task). Critically, both of these assays were designed to be *simple* in order to encourage easier interpretation of their findings, reduce the possibility of confounds (e.g., working memory deficits, cognitive effort), and to enable cross-species translational research.

6.2.1.1. Reward Motivation

Reward motivation has previously been measured using effort-based decision-making tasks such as the EEfRT (section 1.4.5.1; Treadway et al., 2009). Although this task has demonstrated interesting findings in clinical studies (Lawn et al., 2016; McCarthy et al., 2016; Treadway et al., 2012), and is the only reward motivation task currently recommended by the RDoC (Insel et al., 2010), the complex nature of this task makes it difficult to rule out potential confounds such as cognitive ability or reduced cognitive effort (Bonnelle et al., 2015; Cooper et al., 2019; Dean, 2019; Whitton, Merchant, et al., 2020). Consequently, deficits on this task, at least for some people, could be explained by impairments in cognitive ability such as working memory or impaired cognitive effort (i.e., reduced willingness to make cognitive decisions) as opposed to reduced willingness to exert physical effort for reward. As an alternative, we introduce the JORT (Chapter 2), where motivation is operationalized as the exertion of physical force for reward.

We provide proof-of-concept for the JORT as a basic measure of reward motivation across three studies, replicating the primary outcome in both a non-clinical and clinical study (volunteers exerted a linear increase in physical force for higher compared to lower rewards) and demonstrate some construct validity (performance on the JORT positively correlates with another reward motivation task: the EEfRT). The key advantage of the JORT is that it is less likely to be confounded by cognitive functioning and may provide a "purer" measure of reward motivation. In relation to other paradigms reported in the literature, the PRT and handgrip task (Roane et al., 2001; Schmidt et al., 2008) are also promising simple effort-for-reward tasks. However, they have either been criticised for their failure to control for important potential confounds (Chong et al., 2016; PRT) or have not yet been standardised and well-validated and

therefore they are not currently recommended by the RDoC. For example, one potential confound on the PRT is delay discounting: effort is also associated with an increased delay (time taken to obtain the reward; Pessiglione et al., 2018). An advantage of the JORT is that time spent on trials is kept roughly the same thus performance is less likely to be influenced by delay discounting.

6.2.2.2. Reward Learning and Memory

Reward learning and memory tasks in humans (section 1.4.5.3) focus on "online learning" over short periods of time (~ 15 minutes; Wimmer et al., 2018). This markedly differs from preclinical research which often assesses learning and memory over longer time frames (Der-Avakian et al., 2013; Hinchcliffe et al., 2017; Stuart et al., 2013), and may therefore be underpinned by different biological mechanisms (Wimmer et al., 2018). Additionally, all translational paradigms assess the subject's ability to learn the probability that a cue will provide reward. To my knowledge, there are no translational paradigms that measure learning and memory of *different* reward values.

Here, based on a promising rodent task which has reported consistent deficits across multiple putative models of depression (Robinson, 2018), we developed a procedurally similar assay in humans (Chapter 4). In contrast to other reward learning paradigms (Frank et al., 2004; Pizzagalli et al., 2005), this assay measures learning and memory of cues and their associated reward value across five consecutive days. We provided initial face validity for this task in a non-clinical population, with volunteers showing a positive bias (i.e., an intact memory and choice for the high reward images), as predicted. Whilst promising, potential confounds exist, such as the use of higher cognitive strategies to solve the task, which could imply that the task does not tap into the same underlying mechanisms as the rodent version. Therefore, at this stage, caution should be taken in interpreting this task as analogous to the rodent version. Further development of this assay is therefore warranted, ideally limiting the use of written verbal instructions and reducing the

possibility of participants using language to encode and rehearse the stimuli (i.e., by using stimuli that cannot be easily verbalised).

In summary, this thesis provides proof-of-concept for two novel methods, contributing to the need for objective measures of reward components that could be applied across species. Going forward, these tasks will require more rigorous testing of their validity (e.g., predictive and construct validity) and reliability (e.g., test-retest reliability).

6.2.2. Anhedonia and reward processing

Dysfunctional reward processing has been proposed as a promising possible mechanism underlying anhedonia (Halahakoon et al., 2020; Nielson et al., 2020), with increasing evidence supporting an association between the two. However, preclinical research suggests that reward processing is not a unitary construct (Berridge et al., 2009), and accordingly the precise sub-components compromised in anhedonia is unclear. Specifically, whilst people may appear similar at the self-reported symptomatic level, they may have different underlying impairments (Husain & Roiser, 2018). In support of this idea, there is some evidence to suggest that anhedonia in different clinical disorders relate to different aspects of reward-related behaviour (Thomsen et al., 2015). We attempt to address this question in two studies: in a non-clinical population with higher symptoms of anhedonia (Chapter 3) and in a clinically depressed population (Chapter 5). We used a battery of behavioural tasks designed to measure different components of reward processing alongside anhedonia questionnaires to explore this.

In both studies, there was limited evidence of a correlation between behavioural tasks, suggesting that different components of reward (effort-for-reward, effort-based decision-making and reward sensitivity) may also be dissociable in people. Additionally, despite debate in the literature (Amsterdam et al., 1987; Bedwell et al., 2019; Berlin et al., 1998; Dichter et al., 2010), both studies found evidence that anhedonia (measured using the SHAPS) was related to reduced reward sensitivity on the sweet taste test, albeit with weak evidence in the clinical population.

In the non-clinical population (Chapter 3), higher levels of anhedonia (measured using the CPAS) was also related to reduced motivation on an effort-based decision-making task (EEfRT), which replicates the original findings by Treadway et al. (2009). This was not found in the depressed population (Chapter 5), although this could be due to the small sample size, resulting from study termination due to COVID-19.

Interestingly, performance on these two tasks (sweet taste test and EEfRT) did not correlate (individuals with reduced sensitivity to detect sucrose did not display aberrant effort-based decision-making) which lends support for the proposal of heterogeneity within anhedonia (sub-groups of people with different reward-related behaviour), as opposed to a generalised reward impairment. This is an important finding because few studies have assessed multiple domains of reward processing using a battery of tasks in the same sample, and therefore could not adequately address this question.

A key finding in both studies is that there was no evidence that anhedonia was related to reduced motivation on a simple effort-for-reward task (JORT). This is an important contribution, given the dearth of studies examining physical effort exerted for reward in anhedonia (Halahakoon et al., 2020; Pessiglione et al., 2018) and recent definitions of anhedonia proposing a motivational deficit (Thomsen, 2015; Treadway & Zald, 2013). Speculatively, this could suggest that anhedonia is only related to reduced motivation when explicit decision-making involving cognitive effort is required (e.g., explicitly weighing up the cost and benefit of an action; although see Rzepa & McCabe, 2019). Further studies will be required to directly assess this hypothesis. Nevertheless, the discrepancy between these two different types of tasks (decision-making versus actual effort expenditure) highlights the need for researchers to carefully consider their choice of reward motivation assay in future studies given that they could be tapping into slightly different aspects of behaviour.

Finally, we did not see the same pattern of results in the non-clinical (Chapter 3) and clinically depressed population (Chapter 5). In fact, there was no clear evidence of a difference between the depressed and non-

depressed group on any of the behavioural tasks. Whilst we must be cautious in the interpretation of this outcome given the small sample size in the clinical study, if this result replicates in a large sample it could question the extent to which studying a non-clinical population with higher levels of anhedonia can inform us about clinical anhedonia.

In summary, higher levels of anhedonia was associated with tasks designed to measure effort-based decision-making and reward sensitivity. Given the lack of correlations between assays, anhedonia does not appear to reflect a generalised reward impairment.

6.3. Implications for research

6.3.1. Anhedonia questionnaires: similar but not the same

Researchers that have assessed anhedonia have often used a single anhedonia questionnaire such as the SHAPS (Halahakoon et al., 2020 includes examples of studies). However, the present findings indicate that anhedonia questionnaires are not interchangeable. For example, in Chapter 3 the EEfRT was related to the CPAS with less robust evidence for an association with the SHAPS; whereas the sweet taste test was consistently associated with the SHAPS in both the clinical and non-clinical study (although there was weaker evidence in the clinical study). As these anhedonia questionnaires vary in a number of ways (see section 1.3.4), it is not clear why some questionnaires may more robustly correlate with a given behavioural task.

One possible explanation is that the SHAPS focuses more on the consummation of reward ("I would enjoy a cup of tea or coffee or my favourite drink") which is more relevant to reward sensitivity; whereas the CPAS also includes questions on desire or interest ("I have had very little desire to try new kinds of foods") which is more relevant to decision-making (Leventhal et al., 2006; Rizvi et al., 2016). In support of this, Leventhal et al. (2006) reported that the CPAS failed to load (.07) onto a "hedonic capacity factor" when included in a confirmatory factor analysis with the SHAPS and FCPS (which both demonstrated a high loading on this factor: .92 and .68, respectively). This suggests that unlike the

SHAPS, the CPAS does not appear to show high construct validity as a measure of hedonic function (Leventhal et al., 2006). Therefore, researchers should be careful when choosing which self-report measure to use. Failure to do so may result in what appears to be conflicting findings within the field or incorrect null results. Future studies may benefit from employing multiple anhedonia questionnaires to provide a more thorough examination of this symptom and to include newer anhedonia scales to examine their validity (Rizvi et al., 2016).

Although not the focus of this thesis, another interesting finding is that anhedonia scales correlated with each other just as much as they correlated with an apathy scale (Chapter 3). Given that anhedonia and apathy are thought to be distinct conditions, one would expect that anhedonia scales would correlate less with an apathy scale and more with each other (i.e., they would display discriminant validity). This highlights the overlapping nature of these conditions and their assessment (Husain & Roiser, 2018). As proposed by Husain & Roiser (2018), there is a need to dissect these heterogeneous conditions into sub-groups with distinct behavioural deficits (using behavioural tasks). This may help to better decipher the precise impairments experienced by a patient and more appropriately inform treatments (Husain & Roiser, 2018).

6.3.2. Reward motivation: effort exerted versus decision-making.

Reward motivation tasks can broadly be divided into those that assess effort-based decision-making (i.e., explicit choice) or the amount of physical effort exerted for reward. The dissociation between the EEfRT and JORT in relation to anhedonia (Chapter 3) could suggest that these tasks are not tapping into the same underlying mechanisms. This is an important and potentially useful consideration for future studies examining reward motivation because dissociating between these two different types of tasks in the same population of patients who have motivation impairments (e.g., apathy, fatigue, anergia, avolition) may help to get a more nuanced understanding of the underlying changes in behaviour.

Nevertheless, other methodological differences between tasks (such as the presence of a probabilistic cue, type of force exerted), invoke caution in this interpretation. More convincing evidence that these different types of tasks are dissociable may come from a study that matches these paradigms on most other parameters. For example, this could be incorporated into the JORT by *additionally* asking participants to perform explicit decisions between low and high effort/reward options to examine the relationship between choice and force exerted. By doing this, we will be able to examine whether these tasks measure different aspects of motivated behaviour (or if differences between tasks is only attributable to other task features such as the presence of probability cues).

6.3.3. Conceptualisation of anhedonia

Traditionally, anhedonia has been seen as a unitary construct (American Psychiatric Association, 2013). More recently, however, researchers have proposed that the definition of anhedonia should be expanded to reflect its possible heterogeneity (section 1.3.2). Our findings lend support for this theory, as in a non-clinical population we found evidence that behavioural tasks probing different sub-components of reward (reward sensitivity and effort-based decision-making) were associated with higher levels of anhedonia, whilst performance across tasks did not correlate. This suggests that people with higher levels of anhedonia in a non-clinical population may present various profiles of reward-related behaviour. Going forward, further research demonstrating this within a clinical population is needed. For example, a double dissociation in patients - similar to what has been done in the field of memory - may arguably provide more convincing evidence of "sub-groups" within anhedonia; for example, showing that some patients have markedly reduced reward sensitivity, but relatively intact reward motivation, and vice versa (Temple & Richardson, 2004; Vargha-Khadem et al., 1997).

Recently, two definitions of anhedonia have been proposed (Thomsen et al., 2015; Treadway & Zald, 2011; section 1.3.2), which both highlight the heterogeneity of anhedonia, but differ in the precise reward components affected. Both suggest that anhedonia may involve a

motivational and/or consummatory impairment, but differ in their third component: a decisional impairment in the Treadway and Zald definition and a learning impairment in the definition by Thomsen and colleagues (Thomsen et al., 2015; Treadway & Zald, 2011). In this thesis, the working definition of anhedonia was: diminished self-reported pleasure, which may be driven by reduced appetitive motivation, consummatory experience and/or learning. Pertaining to these definitions, we did find evidence that higher levels of anhedonia in a non-clinical population was associated with altered effort-based decision-making (albeit weak) and reduced consummatory experience, as suggested in the Treadway and Zald definition. Interestingly, we did not find clear evidence of reduced motivation (using a simple motivation paradigm), as proposed by both definitions. Future studies will be necessary to further interrogate this null finding using other reward motivation tasks (e.g., PRT and handgrip task), and within clinical populations. Finally, we did not adequately address the possibility of altered reward learning, and so this remains an open and essential question. Based on the findings obtained from this thesis, the working definition of anhedonia could be more narrowly defined as: diminished self-reported pleasure, which may be driven by reduced motivational decision-making, sensitivity to reward and/or learning. This definition focuses the motivational impairments on decision-making (as opposed to actual effort exerted) and more narrowly defines the consummatory impairments as reduced sensitivity to detect rewards (as opposed to reduced liking of reward).

In sum, the data presented here do not provide compelling evidence in favour of either definition, but they do support the claim that anhedonia measured using self-report scales is heterogeneous (Treadway & Zald, 2011). It is critical to also note that the findings presented here are predominantly based on a *non-clinical population* with higher levels of anhedonia (i.e., individuals who report less interest or pleasure). It is unclear whether higher scores on anhedonia scales in a non-clinical population qualitatively (or just quantitively) differs from anhedonia reported in disorders such as depression. Going forward, it will be crucial

to thoroughly examine anhedonia across multiple psychiatric populations using a battery of tasks in the same individuals.

6.3.4. Preclinical anhedonia research

Based on the earlier definition of anhedonia as a loss of pleasure, anhedonia research in rodents has concentrated on consummatory tests (such as the sucrose preference test; Admon & Pizzagalli, 2015). However, the findings in this thesis support the theory that symptoms of anhedonia are associated with broader reward deficits, including effort-based decision-making (Treadway & Zald, 2013). Thus, effort-based choice tasks may provide an additional useful tool in preclinical anhedonia research (Salamone et al., 2018). Interestingly, given that we did not find any evidence of reduced motivation on a basic motivation assay (amount of force exerted for reward) in relation to anhedonia, this could suggest that effort-based choice tasks are *more sensitive* to the motivation impairments present in anhedonia, than basic effort-for-reward tasks such as the progressive ratio task - which is more commonly used in animal research.

Going forward, the heterogeneity of anhedonia in clinical research highlights the critical need to measure *other* aspects of reward-related behaviour in anhedonia research (Admon & Pizzagalli, 2015). Given the promising findings of the reward learning assay in many putative models of depression (Robinson, 2018), this provides a great example of a paradigm that could be used. Other promising examples are the RBPRT (Der-Avakian et al., 2013; Wooldridge et al., 2020), probabilistic reversal learning task (Bari et al., 2010) and the judgement bias test (Hales et al., 2016). Moreover, a key advantage of these assays is that many of them also have procedurally analogous human versions (Aylward et al., 2019; Cools et al., 2002; Pizzagalli et al., 2005) enabling the possibility for translational research.

6.4. Implications for clinical practice

Our findings support the hypothesis that people with higher levels of anhedonia display various reward processing profiles. As different

domains of reward processing are suggested to differ neurochemically and neuroanatomically (Berridge & Robinson, 2003), this line of research could have important implications for treatment (Treadway & Zald, 2011). For example, patients with reduced reward motivation on an effort-based decision-making paradigm may respond better to a dopaminergic drug than patients who have a reduced consummatory experience of reward (Soder et al., 2020; Treadway & Zald, 2011; Wardle et al., 2011). However, future research will need to demonstrate similar findings to those presented here in clinical populations *and* show evidence that altered reward processing plays a causal role in the development and maintenance of clinical anhedonia (section 6.6).

6.5. Limitations and Challenges

6.5.1. Methodological

6.5.1.1. Potential confounds

One limitation of this thesis is the presence of potential confounds, and as a result it is possible that altered performance in some tasks is not related to changes in reward processing *per se*. Specifically, it could be due to other impairments or reflect a general blunting (regardless of valence). For instance, the sweet taste test is used in the human literature as a measure of reward sensitivity. However, differences on this task could be due to a simpler impairment (e.g., altered sensory receptors), as opposed to a higher-order reward deficit in the brain (although see Han et al., 2020; McCabe, 2016). Interestingly, there has been very little work on the mechanisms which may underpin the relationship between affective state and taste and so this remains an open question (Heath et al., 2006). Another possibility is that reduced sensitivity on this task could reflect a general impairment that is not specific to reward. To address this, future studies would benefit from including additional negative controls such as an aversive taste test (e.g., quinine). Including negative controls could also provide an appealing approach to help distinguish between similar but putatively different conditions such as apathy (Husain & Roiser, 2018).

6.5.1.2. Sample size and power

The sample size chosen for most of the experiments in this thesis were based on power calculations to detect a medium-to-large effect size (e.g., Cohen's *d* =.63 in Chapter 5). However, for many of the included studies, there was limited previous research to determine the effect size of interest and so these studies were calculated taking into consideration resource availability. Consequently, it is possible that any null findings in this thesis could be because the true effect size is smaller than the effect size we were powered to detect. This means that the studies are underpowered to refute a smaller effect size (if one is present). Additionally, some experiments failed to reach the planned sample size and therefore caution must be taken when interpreting these findings given that they are underpowered to detect the effect size of interest. This was predominantly driven by drop-out during the experiment or *a priori* exclusion criteria. To account for this, the number of participants who drop-out or meet exclusion criteria should be estimated and incorporated into the chosen sample size to ensure the target sample size is still met.

6.5.1.3. Type of reward

Consistent with most human reward processing studies, I have *primarily* used money as a reward. Although there are advantages of using money (universally valued and easily manipulated), there are some inherent limitations of over-reliance on money in the human literature. First, there is evidence that primary (e.g., food, drink) and secondary rewards (e.g., money) recruit at least partially dissociable brain systems (Sescousse et al., 2013). This is an important consideration for translational research because preclinical studies use primary rewards such as food. Second, financial concerns may be a potential confound in reward processing studies. For example, we found evidence that concerns about money influenced performance on the reward learning and memory task: people with higher finance concerns demonstrated "better" performance. Interestingly, self-reported income level did not influence performance, and therefore questions pertaining specifically to worries/concerns about

money may serve as useful controls in studies using monetary rewards. As a result, future research would benefit from also looking at other types of rewards, or at least controlling for this potential confound in their research.

6.5.1.4. Translational validity

Some of the tasks used in this thesis are based on rodent measures. There are many advantages of this approach such as increasing the likelihood of tapping into similar components of reward and the increased potential for translating findings across human and rodent studies (Aylward et al., 2019). However, it is crucial to note that the translational validity of these paradigms is still sparse (Der-Avakian & Pizzagalli, 2018). This means that whilst these tasks attempt to measure similar constructs in humans and rodents, it is possible that they are not recruiting the same cognitive and neural systems. Further studies are needed to further interrogate their translational validity not only in terms of face validity, but also predictive and construct validity (Pike et al., 2021).

6.5.2. Conceptual

6.5.2.1. Terminology

There is inconsistent and often overlapping terminology in the reward processing literature (Calabrese et al., 2014; Nielson et al., 2020). Whilst I have based my definitions on those used in preclinical research, the terminology within the field varies. For instance, I have referred to the EEfRT as a measure of reward motivation (Thomsen, 2015), whereas in the RDoC the EEfRT is now located under the label "reward valuation" (Insel et al., 2010). This is a fundamental obstacle because it makes dissection of reward processing components, and comparison across studies, very challenging (Nielson et al., 2020). Convergence in terminology would therefore be beneficial to ensure consistency and easier comparison across studies.

Inconsistent terminology likely stems, in part, from the fact that most components of reward (e.g., motivation) and paradigms designed to assess them are complex and likely require many aspects of behaviour. Future work using computational modelling (Husain & Roiser, 2018; Huys et al., 2013; Nielson et al., 2020; Pessiglione et al., 2018; Robinson & Chase, 2017), carefully designed behavioural assays, and the inclusion of behavioural controls within studies, may help to elucidate the precise behavioural impairments present in some paradigms and guide terminology appropriately. As well as inconsistent terminology, there is also overlapping terminology whereby the same term is used to describe potentially different behaviour (Nielson et al., 2020). Nevertheless, it is possible that broad terms such as "reward sensitivity" could become parsed (e.g., reward detection versus hedonic response) with further research efforts demonstrating dissociations.

6.5.3. Generalisability

As mentioned in previous chapters, many studies in this thesis recruited student populations (except Chapter 5). This is a limitation because students are not representative of the general population, which limits the external validity of these results (Henrich et al., 2010). This means that the findings reported in many of these studies may not generalise to other populations (e.g., older age, lower education attainment, lower socioeconomic status). However, mental health problems are a pressing concern in student populations (Storrie et al., 2010) and thus the findings of these studies are still highly relevant and important. It could also be argued that including a more diverse population with the same sample sizes used here may mask potentially important findings which are relevant to some sub-groups.

6.6. Future perspectives

One key area for future research is to invest effort into the rigorous *validation* of reward-processing tasks. Specifically, this involves optimising and standardising task parameters, checking the assays validity (construct, predictive, translational) and reliability (test-retest),

and removing other potential confounds where possible. This is *crucial* yet often over-looked, which may partly be due to demands on researchers to provide exciting findings with novel techniques (e.g., fMRI, optogenetics ; Niv, 2020). This is unfortunate, as it reduces confidence in the behavioural output (which is often a key element of those study designs anyway) and hinders our ability to conduct valid translational research.

Another area for future research is to address whether dysfunctional reward processing plays a *causal* role in the onset of clinical anhedonia (Nielson et al., 2020). One way to tackle causality may be longitudinal studies that measure components of reward processing and anhedonia (using anhedonia questionnaires) across multiple time points (Nielson et al., 2020). This would enable us to investigate whether dysfunctional reward processing early in life increases future risk of anhedonia in clinical populations. It is also possible, however, that deficits in reward processing are not a cause but rather a correlate (exists alongside) or consequence (emerges due to) of clinical anhedonia (Nielson et al., 2020). Although in these cases reward processing may not be a promising treatment target for anhedonia, it could still provide a useful biomarker of treatment response (Nielson et al., 2020). It is also important to note that although a transdiagnostic approach is valuable (Reilly et al., 2020), it is possible that the relationship between clinical anhedonia and abnormal reward processing may differ depending on the disorder. There are excellent longitudinal birth cohorts which could help to address this question (such as Avon Longitudinal Study of Parents and Children; ALSPAC)(Boyd et al., 2013). However, to my knowledge, there are *currently* very few reward processing and anhedonia measures included in these birth cohorts - inclusion of these measures in cohorts such as ALSPAC would be fruitful.

To complement the methods used here and to provide ecological validity of the reward motivation tasks (JORT and EEfRT), it would be useful to investigate reward motivation in a naturalistic environment (Frey et al., 2019; Moran et al., 2017). One way to do this would be to use Ecological Momentary Assessments (EMA), which repeatedly measures a person's

affect and/or behaviour in their natural environment (Moskowitz & Young, 2006; Stone & Shiffman, 1994). For example, one could examine whether poorer motivation on a laboratory task (JORT or EEfRT) predicts poorer motivation in real life (e.g., by measuring self-reported motivation several times a day over a few weeks) or whether motivation in everyday life is impaired in people with clinical anhedonia. However, this method relies on self-report measures which suffer numerous shortcomings (section 1.3.5). Thus, objective measures of motivation within real-life settings would be fruitful, albeit challenging. An example of such an approach could include indirect examination of motivation within homes designed to monitor and assess behaviour using sensors (e.g., Sensor Platform for Healthcare in a Residential Environment; SPHERE)(Zhu et al., 2015).

Finally, there is exciting research on the efficacy of rapid acting antidepressants (e.g., ketamine) for treatment-resistant depression, and in particular the symptom anhedonia (Lally et al., 2014; Rodrigues et al., 2020). This is timely given the well-reported failure of conventional antidepressants in the treatment of this symptom (McMakin et al., 2012; Uher et al., 2012). However, the precise behavioural and cognitive mechanisms underpinning ketamine's antidepressant effect remains elusive. Subsequent progress in this endeavour will likely benefit from objective behavioural tasks, such as the ones mentioned in this thesis, designed to measure specific behavioural constructs (Robinson, 2018). Indeed, this avenue is starting to be addressed in the preclinical literature (Griesius et al., 2020; Hales et al., 2017; Wilkinson et al., 2020; Wooldridge et al., 2020), which has found promising results in assays designed to assess reward learning and reward sensitivity (Robinson, 2018; Wooldridge et al., 2020). This should be extended to humans because it may provide insight into how these drugs are effective.

6.7. Conclusion

Despite increasing evidence that anhedonia is related to aberrant reward processing, the precise deficits remain unclear. Using a battery of behavioural paradigms, this thesis aimed to shed some light on this issue by examining multiple domains of reward processing in people with

higher levels of anhedonia. In line with preclinical work, we provide evidence that different components of reward may be dissociable in people (effort-for-reward, effort-based decision-making and reward sensitivity), and support for the theory that anhedonia (as measured using questionnaires) is heterogeneous. Going forward, a challenge within the literature will be to further refine and fractionate reward processing and to provide further evidence that human tasks align with preclinical work (by encouraging translational research), with an aim to develop new targeted treatments.

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