Exploring individual differences in anhedonia using psychometric, behavioural and electrophysiological methods

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Declaration

Declaration of Authorship

I, Éilish Duke, hereby declare that this thesis and the work presented in it is entirely my own. Where I have consulted the work of others, this is always clearly stated.

Signed: _____ _____

Date: 02 / 01 / 2019

Abstract

Depression affects over 300 million people and is a leading burden of illness worldwide. Despite its prevalence, highly effective treatments for depression are lacking. The absence of efficacious treatment may be due to poor understanding of the symptoms underpinning depression. One important indicator of poor response to treatment is the symptom, anhedonia. Anhedonia presents as impaired reward processing, particularly approach motivation, and is a transdiagnostic symptom common to depression, schizophrenia, Parkinson's Disease and addiction. Individual differences in anhedonia reveal a trait-like stability for this construct, suggesting clinical utility as a marker of treatment response and psychopathology. However, the putative utility of anhedonia is undermined by inconsistencies and inaccuracies in the measurement of this construct. This thesis aimed to investigate the measurement of motivational processes in anhedonia and sought to develop a new self-report measure, sensitive to the multifaceted nature of individual differences in anhedonia. Two initial studies sought to examine the convergent validity of neural (EEG cerebral asymmetry), behavioural and psychometric measures of approach and withdrawal motivation. These studies suggested that, contrary to much of the literature, these measures are assessing discrete sub-components of approach and withdrawal motivation. Two subsequent studies sought to develop and validate a self-report measure of multidimensional anhedonia. The Goldsmiths Anhedonia Measure (GAME) yields a four-factor structure, sensitive to individual differences in interpersonal, emotional, sensory and novelty-seeking aspects of reward processing. Finally, the putative causal relationship between perceived stress and anhedonia was examined. Reflecting the multi-dimensional nature of anhedonia suggested by prior studies, perceived stress predicted anhedonia only in interpersonal, emotional and anticipatory domains (but not sensory, novelty-seeking or consummatory areas). These findings highlight the need to refine measurement of motivational processes in anhedonia to better characterise individual differences in treatment response and contribute to the theoretical understanding of a multifaceted reward "wanting" process.

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Dedication

To my mother, Marion, and in memory of my father, Johnnie, for starting me off with Henny Penny.

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List of publications relevant to this thesis

Duke, É., Schnuerch, R., Heeren, G., Reuter, M., Montag, C. & Markett, S. (2018). Cortical alpha asymmetry at central and posterior – but not anterior – sites is associated with individual differences in behavioural loss aversion. *Personality and Individual Differences*, 121, 206 – 212.

This publication is adapted from Chapter 3.

The data in this chapter were collected for me by my collaborators S. Markett and G. Heeren as part of a larger body of research.

List of presentations relevant to this thesis

Duke, É., Schnuerch, R., Heeren, G., Reuter, M., Montag, C. & Markett, S. (2017). *Cortical alpha asymmetry at central and posterior – but not anterior – sites is associated with individual differences in behavioural loss aversion.* Conference presentation at 13th biennial conference of the International Society for the Study of Individual Differences (ISSID), Warsaw, Poland.

Duke, É., Stavrou, M., Smillie, L. D., Pickering, A. D., & Cooper, A. J. (2015). *Individual differences in relative left frontal cortical activity and willingness to expend effort for reward.* Conference presentation at 12th biennial conference of the International Society for the Study of Individual Differences (ISSID), London, Ontario. *Abstract published in Personality and Individual Differences, 101, p. 474-475.*

Duke, É., Stavrou, M., Smillie, L. D., Pickering, A. D., & Cooper, A. J. (2015). *Individual differences in relative left frontal cortical activity and willingness to expend effort for reward.* Poster presented at the 6th annual conference of the British Society for the Psychology of Individual Differences, Nottingham, UK.

Chapter 1

Introduction

Overview

This introductory chapter will present the core concepts and literature central to the thesis and will outline the aims and hypotheses of the empirical chapters that follow. First, the term anhedonia – thought to reflect impairments in reward wanting or liking – will be introduced and critically examined. Its role in depression and its relevance as a potential trait marker for depression will be emphasised. Second, aspects of reward processing will be outlined, with particular emphasis on approach and withdrawal motivation. Two core theories related to this literature: The reinforcement sensitivity theory (Gray, 1972; Gray & McNaughton, 2000) and Davidson's (1992) theory of motivational direction will be detailed and discussed. Third, the neurobiological bases for approach motivation will be outlined, with a particular emphasis on the role of dopaminergic processes. Fourth, disparities between our conceptualisation and measurement of anhedonia will be highlighted. Fifth, some consideration will be given to putative causal factors leading to higher levels of anhedonia. This section will focus on the diathesis-stress model discussed by Pizzagalli (2014) and a putative role for inflammation as a driver of dopaminergic motivational impairments in depression. Finally, the programme of research discussed in this thesis will be outlined, including the specific aims and hypotheses of each chapter. This chapter does not seek to provide a comprehensive review of this diverse range of topics, rather, we hope to provide the reader with a concise and contemporary overview of the most essential research in these areas and demonstrate the relevance and import of the studies that follow.

1.1 Depression: a health burden

Depression is rapidly becoming a leading burden of illness in society (World Health Organisation (WHO), 2018). Affecting over 300 million people worldwide (WHO, 2018), Major Depressive Disorder (MDD) has a lifetime prevalence of 16.2 per cent (Kessler et al., 2003). Currently positioned as the fourth leading cause of disability-adjusted life years (DALYS; an attempt to objectively measure the overall burden of a

disorder, based on its impact on years lost to disability, illness or early death), MDD is projected to become the second most disabling condition by 2020, behind only ischemic heart disease (Murray & Lopez, 1996). Further impacting patients is the lack of success with which depressive disorders are treated (Warden, Rush, Trivedi, Fava & Wisniewski, 2007). Despite the existence of a plethora of treatments, including pharmacological, e.g. selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), behavioural, e.g. cognitive behaviour therapy (CBT), and traditional talking therapies, highly effective treatments for depression are lacking. Current estimates of treatment efficacy are, at best, 50 - 60 per cent (Cipriani et al., 2009; Rush et al., 2006; Trivedi et al., 2006) and first-time treatments succeed as little as one-third of the time (Rush et al. 2006). Clinically significant differences can be observed in the response to different antidepressant drugs (Cipriani et al., 2009) and patients often try two or three different drugs before an adequate treatment is found (Montgomery, Nielsen, Poulsen & Häggström, 2014; Rush et al., 2006). Even after trying multiple different treatment strategies, a proportion of patients will not respond to treatment. Current estimates suggest that these non-responders account for between 20 to 50 per cent of patients presenting for treatment (Akil et al., 2018; Berlim & Turecki, 2007; Fava, 2003). Thus, efforts to clarify our understanding of the symptoms of depression and of predictors of anti-depressant response are a clear research priority.

1.2 Anhedonia: what's in a name?

One important indicator of a poor response to treatment is the presence of the symptom, anhedonia (Nutt et al., 2006; Shelton & Tomarken, 2001; Spijker, Bijl, de Graaf & Nolen, 2001; Uher et al., 2008, 2012), which is experienced by approximately 37 per cent of patients with MDD (Pelizza & Ferrari, 2009). Anhedonia is a cardinal symptom of depression; one of two symptoms required to receive a diagnosis of MDD (see table 1.1). Anhedonia is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM 5; American Psychological Association (APA), 2013), as *"A loss of interest and enjoyment in pleasurable activities"* (APA, 2013, p. 163). However, myriad difficulties exist with this definition and with the concept of anhedonia more generally. Anhedonia is a transdiagnostic symptom, observed across depression, schizophrenia, Parkinson's disease, post-traumatic stress disorder (PTSD) and

addiction. The study of anhedonia within these disorders has largely evolved into separate literatures, which has resulted in significant discrepancy in the nomenclature defining anhedonia in different contexts (Cooper, Arulpragasam & Treadway, 2018; Treadway & Zald, 2011; 2013). Multiple different terms are used to refer to anhedonia or related phenotypes, e.g. apathy, avolition, anergia. Indeed, the DSM itself differentially defines anhedonia depending on the context of depression or schizophrenia. In contrast to the above definition in MDD, anhedonia in schizophrenia is defined as *"the decreased ability to experience pleasure from positive stimuli or a degradation in the recollection of pleasure previously experienced"* (APA, 2013, p. 88). These definitions not only emphasise different facets of anhedonia, i.e. the emphasis is on motivation and "liking" rewards in depression, but is on the experience and memory of pleasure in schizophrenia, but also conflate several distinct constructs and treat them as equivalent, e.g. "liking" rewards and "wanting" them.

Table 1.1: DSM 5 criteria for the assessment of MDD or a depressive episode: one of two symptoms from column A must be present for a two-week period, as well as five or more from column B.

A	B
Depressed Mood Loss of interest and enjoyment in pleasurable activities (anhedonia)	Psychomotor agitation / retardation Fatigue or loss of energy Ideas of guilt and worthlessness Diminished ability to concentrate Disturbed sleep Change in appetite Ideas of self-harm / suicide

1.3 The constellation of reward processing domains

Such discrepancies in the nomenclature related to anhedonia have led to substantive difficulties in measuring anhedonia and in translating pre-clinical models of anhedonic behaviours for study in humans (Salamone & Correa, 2012; Berridge & Robinson,

1998). Deficits in reward processing occur across a variety of domains in DSM-5 diagnoses. Given the prevalence of disorders such as depression and schizophrenia, and the centrality of reward processing deficits to these disorders, abnormal reward processing is arguably one of the most common symptoms of psychopathology in humans (Zald & Treadway, 2017). Such deficits are unlikely to be homogenous across disorders and different reward processing deficits may lead to the development of similar phenotypes across disorders. Compounding this difficulty, the term "reward processing" is an umbrella term for a constellation of features of motivated behaviour, which occur across different phases. Despite this, the term is often used interchangeably to refer to reinforcement, primary motivation or hedonia (for a nuanced - and humorous - discussion see Cannon & Bseikri, 2004; Salamone & Correa, 2012). Figure 1.1 illustrates these phases and this section will attempt to integrate and clarify some of these semantic issues to introduce the relevant vocabulary for this thesis.

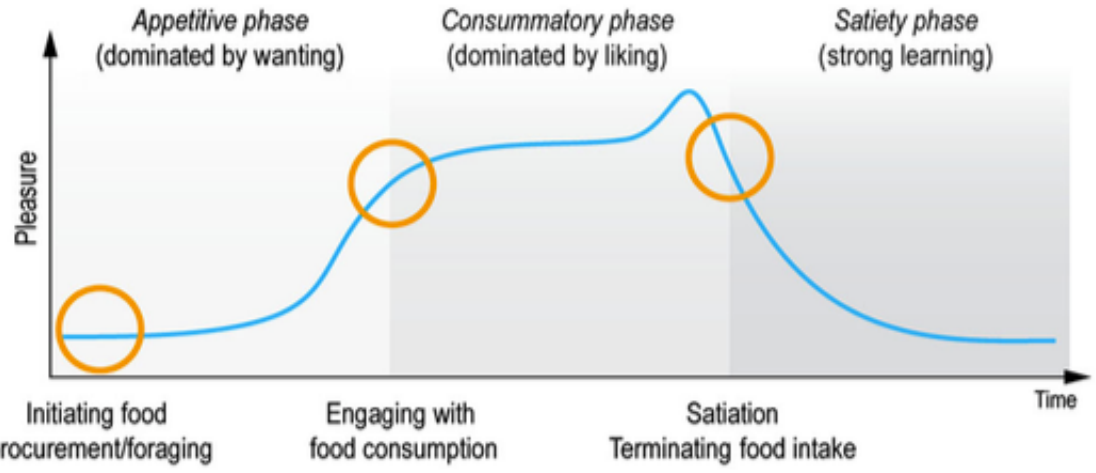

Figure 1.1: From Rømer Thomsen, Whybrow and Kringelbach (2015): This figure outlines the reward cycle through the example of food. The initial phase of reward is characterised by wanting a reward and encompasses behaviours that are motivated toward the reward, e.g. anticipation of the reward value and mobilising the effort needed to procure the reward. The next phase of the reward cycle is focused on consummation of the reward and is characterised by liking or enjoyment of the reward. Behaviours during this phase are focused on consuming and enjoying the reward once it has been attained. The final phase of the reward cycle is related to the learning. During this phase, the organism reaches satiety (in the case of a food reward) and learns the value associated with the obtained reward. In a healthy organism, this learning will inform subsequent cycles of reward processing, e.g. when the organism is presented with similar rewards in the future.

Motivated behaviour has both directional and phasic dimensions (Salamone & Correa, 2012). Behaviour is directed towards a desired goal or stimulus, or it is used to withdraw from or avoid an aversive stimulus. Taking food as a desirable reward, we can see that motivated behaviour occurs across multiple phases. Initially there is an activational component, in which the organism experiences appetitive desire or "wanting" for the reward and works to obtain the food. As there is typically some physical or psychological distance between the organism and the reward, some level of effort is usually required to obtain the food, thus, the organism may need to press a lever or navigate a maze or some obstacle to procure the food. This phase involves some overlap between the psychological elements of wanting or valuing the reward and the physical requirements necessary to obtain the reward (e.g. motor control and energy). Finally, there will be the consummation of the reward; the organism obtains the food and consumes it. This, in turn, leads to satiety, at which point the reward becomes less palatable, e.g. because the organism is full or fatigued. Throughout the reward cycle, the organism will also learn something about the reward process, e.g. by considering the value of that reward and the relative effort they expended to obtain it or learning to pair a given cue with a particular outcome. This learning will inform their future reward-related behaviour when they encounter similar rewards and / or situations. As highlighted in Figure 1.1, a variety of terms are associated with these disparate phases of reward processing: the initial stage may be termed "appetitive", "approach", "seeking", "anticipatory", "instrumental" or "wanting"; the second stage is characterised by effort expenditure or willingness to work for the reward, but is typically encompassed in this initial approach stage, the aim of which is to increase the likelihood of obtaining the reward; the third phase sees completion of reward-seeking, and is usually referred to as the "consummatory" or "liking" phase; finally, the fourth stage is considered "satiation" or "learning". This thesis will focus on the initial stage of "approach" (or, in the case of aversive stimuli, "avoidance") and willingness to expend effort. The terms approach motivation and reward wanting will be used interchangeably and withdrawal motivation will be the preferred term for behaviours focused on avoiding undesirable stimuli.

1.4 Anhedonia: Loss of interest versus loss of pleasure.

A comprehensive summary of reward processing deficits associated with anhedonia is beyond the scope of the present work. A discussion of these deficits is provided by Pizzagalli (2014). This section will focus on disentangling aspects of reward wanting and reward liking in anhedonia. This focus is due to the conflation of these aspects of reward processing in clinical practice (e.g. as in the DSM-5 definition of anhedonia in MDD). This conflation finds little support in the neurobiological evidence discussed below, which suggests that these processes are, at least partially, dissociable (see section 1.8). Similarly, the clinical research in this area provides little support for this definition. Research on patients with depression suggests that specific deficits related to anticipatory pleasure and / or motivational processes may represent anhedonia more accurately than traditional conceptualisations of the construct as a combination of "wanting" and "liking" impairments.

Original definitions and theories of anhedonia emphasised a loss of consummatory pleasure. From Ribot's (1896) definition of anhedonia as a loss of pleasure to Wise's (1980) dopamine deficiency hypothesis of anhedonia, which argued that reduction in dopamine transmission resulted in an organism's inability to extract pleasure from a stimulus, the absence of pleasure was firmly linked to anhedonia. Reflecting this early emphasis on consummatory pleasure (i.e. "liking" of rewards), most self-report measures of anhedonia focus on deficits in reward liking (see table 1.2 and section 1.9). However, basic and clinical research provide limited evidence for deficits in reward liking in anhedonia. Additionally, although aberrant dopaminergic processing does seem to be important in anhedonia, this has been more closely linked to that first stage of reward processing, wanting, rather than liking.

Human analogues of rodent paradigms such as the sweet taste test, often find intact "liking" in humans with MDD or schizophrenia (Berlin, Givry-Steiner, Lecrubier & Puech, 1998; Dichter et al., 2010). Rodent models of the sweet taste test typically provide the creature with a choice between consuming a sweet sucrose solution or drinking plain water. Preference is assessed by the volume of liquid consumed by the rodent and is typically thought to indicate the ability to experience pleasure. Thus, a preference for plain water over the sucrose solution is thought to reflect "liking" deficits

or consummatory anhedonia (Willner, 2005). Crucially, Willner, Muscat & Papp (1992) have demonstrated that this preference for sucrose-infused water versus plain water is unrelated to calorie content and does not reflect an overall decrease in liquid consumption. By considering the relative volume of sucrose solution (compared to plain water), this paradigm allows researchers to assess deficits in liking sweet rewards. Berlin et al. (1998) observed similar hedonic responses to sucrose in patients with MDD and schizophrenia compared to healthy controls, despite both patient groups showing relatively higher scores on self-report measures of anhedonia. Subsequent treatment of the MDD group with anti-depressants bore no impact on patients' liking of sucrose (though did correlate with an increase in the perceived pleasantness of plain water). Similarly, Dichter et al. (2010) found no difference in response to a human analogue of the sweet taste test between a group of patients with MDD and healthy controls across a period of 12 weeks. This work suggests that anhedonia in depression and schizophrenia is relatively independent of impairments in reward liking.

In contrast, impairments in reward "wanting" – particularly in patients' willingness to expend effort for rewards – have frequently been observed. Sherdell, Waugh and Gotlib (2012) observed a dissociation between enjoyment of humorous cartoons and willingness to expend physical effort to see these cartoons in a group of patients with MDD, relative to healthy controls. While both healthy controls and patients with MDD rated the cartoons as equally amusing, this "liking" of the cartoons only predicted willingness to exert effort (by clicking a computer mouse on an on-screen target) to see the cartoons again for the healthy controls. The authors concluded that this finding implied a discrete deficit in anticipatory processes in patients with MDD, whereby they underestimated future enjoyment of a reward, despite demonstrating intact liking once the reward was received.

A body of work founded on the analogous Effort Expenditure for Reward Task (EEfRT; Treadway, Buckholtz, Schwartzman, Lambert & Zald, 2009) offers a more nuanced picture of anhedonic deficits. The EEfRT is a human analogue of the effort paradigms employed by Salamone and colleagues (1997; 2002; 2007 - see section 1.8.2.3). The EEfRT is a computer-based game, in which participants are offered the option of a "hard" task or an "easy" task. The easy task is associated with a fixed reward of a low sum of money (usually £1 / $1 / €1 or the equivalent). The participant is required to

press a key (using a QWERTY keyboard) 10 times within 7 seconds, using the index finger of their dominant hand to "win" the financial reward. In contrast, choice of the "hard" task, affords the participant the option to win a larger financial reward, varying in value from ~£1.24 (or equivalent) to approximately £4.05. To "win" on this trial, the participant must use the pinkie (little) finger of their non-dominant hand to press a button 100 times in 21 seconds; a task requiring substantially greater physical effort. Crucially, "winning" on the task does not guarantee that the participant will receive the reward. The likelihood of receiving the reward (upon successful completion of the task) is contingent on a categorical probability value of that particular task trial (usually 12%. 50% or 88%, but some variants exist; see, e.g. Yang, Huang, Zhu, Wang, Cheung, Chan & Xie, 2014).

Using the EEfRT, several researchers have demonstrated a reduced tendency in patients with anhedonic disorders, e.g. depression and schizophrenia, to choose the hard task, particularly when the likelihood of receiving the reward is low (i.e. 12%) (Barch, Treadway & Schoen, 2014; Treadway, Bossaller, Shelton & Zald, 2012; Yang et al., 2014). This reduced willingness to expend effort for reward has been explicitly linked to anhedonic symptoms, so that fewer hard task choices of the EEfRT are related to more severe negative symptoms in schizophrenia (Barch, Treadway & Schoen, 2014), and higher scores on self-report measures of anhedonia, particularly items sensitive to anticipatory processes (Treadway et al., 2012; Yang et al., 2014).

1.5 Refining anhedonia: a trait-based, research-led approach

Individual differences in both willingness to expend effort for reward and anticipatory processes more generally have also been observed, suggesting that anhedonia may best be conceived as a trait-like dimension, on which extreme scores place individuals at risk of developing psychopathology. Treadway et al. (2009) observed individual differences in healthy controls on willingness to choose the hard task on the EEfRT and this variation was associated with variance in self-reported trait anhedonia, as measured by the Chapman scales (Chapman, Chapman & Raulin, 1976). More broadly, levels of anhedonia are elevated in first-degree relatives of people with depression compared to the general population (Liu et al., 2011; 2016), and relatives of patients with MDD show altered neural responses when processing rewards and punishments (McCabe,

Woffindale, Harmer & Cowen, 2012). Shared genetic factors were found to account for approximately 46 per cent of the variance in hedonic capacity in a twin study (Bogdan & Pizzagalli, 2009), suggesting substantial heritability for anhedonia. Meanwhile, levels of anhedonia strongly predict the onset of depression one year later (Dryman & Eaton, 1991) and, despite remission of MDD, levels of anhedonia tend to stay reasonably stable (Liu et al., 2011). Taken together, this work suggests anhedonia is better viewed as a trait-like dimension, rather than a specific symptom linked to psychopathology. Thus, the investigation of individual differences in aspects of reward processing pertaining to anhedonia is a key area for research seeking to better characterise and measure this phenotype.

This understanding of anhedonia, grounded in research on its mechanistic underpinnings, reflects a recent change in psychology and psychiatry, aimed at refining our understanding and classification of mental disorders based on core brain-behaviour dimensions (Cuthbert & Insel, 2013; Insel et al., 2010; Insel & Cuthbert, 2015). This initiative, the Research Domain Criteria (RDoC) was launched by the National Institute of Mental Health to address issues with current classification systems, such as the problematic symptom-based diagnoses used in taxonomies such as the DSM-5 (see Insel et al., 2010 for a discussion). Taking MDD as an example, the DSM-IV-TR (APA, 2000) and DSM-5 (APA, 2013) guide diagnosis of depression based on the presence of five or six out of nine symptoms, respectively. In practice, this allows for patients to be given the same diagnosis (and treatment), while only sharing one (or, using the DSM-5, three) symptoms, which may be as generic as disturbances in sleep pattern, change in appetite or fatigue. This heterogeneity in diagnosis may mask vital symptom-specific associations, both within and between disorders (see, e.g. Lambert, Da Silva, Ceniti, Rizvi, Foussias & Kennedy, 2018). One such example in the case of depression and schizophrenia is individual differences in anhedonia, which may have unique associations with certain symptom clusters. In an attempt to address such heterogeneity, the RDoC takes current understanding of brain-behaviour relationships as a starting point and links these dimensions to the presentation of specific symptoms in an effort to refine diagnostic criteria and improve treatment efficacy (e.g. given the role of anhedonia as a predictor of anti-depressant treatment response – see section 1.1). The current programme of research is grounded within this approach and focuses on a core facet of the RDoC – the Positive Valence System, which considers distinct profiles of

reward processing and approach motivation central to certain psychiatric disorders (see Nusslock & Alloy, 2017 for an overview) and argues for the integration of neural, behavioural, genetic and psychometric measurement of symptoms, to better characterise their phenotypes.

A complementary approach regards anhedonia – or approach-related reward processing deficits more broadly – as a putative endophenotype or trait marker of MDD. Endophenotypes are a contentious shorthand for latent downstream traits related to clinical phenotypes. They can be perceived as a bridge between the biological (dominantly genetic and neural) bases of the disorder and its observable aspects. According to Gottesman and Gould (2003), eligible endophenotypes must: a) be specific to a given condition; b) demonstrate heritability; c) show state independence, i.e. trait-like stability over time, independent of illness status or treatment; d) be cosegregated, i.e. occur more frequently – or at a higher level – in those affected with a specific disorder, relative to their unaffected family members; e) have a familial association, i.e. the endophenotype should be more common among the family of an affected person, relative to the general population; and f) be biologically and clinically plausible.

Anhedonia has long been posited as a putative trait marker for depression (e.g. Meehl, 1975). The recent resurgence of interest in anhedonia has provided considerable support for its role as an endophenotype for depression (Berghorst & Pizzagalli, 2010; Hasler, Drevets, Manji & Charney, 2004; Hasler & Northoff, 2011; Vrieze & Claes, 2009). Adherents of this approach argue that anhedonia fulfils most of the criteria discussed by Gottesman and Gould (2003). A full discussion of whether anhedonia fulfils these criteria is provided by Berghorst and Pizzagalli (2010), but is briefly summarised here. Anhedonia demonstrates substantial heritability (criterion b). Estimates of the heritability range from 22 to 67 per cent, depending on the measurement of anhedonia, e.g. specific self-report questionnaire or behavioural measure (Bogdan & Pizzagalli, 2009; Hay, Martin, Foley, Treloar, Kirk & Heath, 2001; Heath, Cloninger & Martin, 1994; Keller & Nesse, 2005; Kendler & Hewit, 1992; Linney, Murrag, Peters, MacDonald, Rijsdijk & Sham, 2003; Ono et al., 2002). The state independence or trait-like nature of anhedonia (criterion c) is a further source of debate and measurement error in the literature. While the DSM-5 conceptualises anhedonia as a state-based

symptom of MDD, much of the research suggests trait-like independence in this construct. As noted above, levels of anhedonia strongly predict the onset of depression one year later (Dryman & Eaton, 1991) and tend to remain reasonably stable even once MDD is in remission (Liu et al., 2011). Taken together, this suggests a trait-like nature for anhedonia. Reflecting this stability, many self-report measures of anhedonia capture a trait-like dimension, rather than state-based measurements (see table 1.2). By emphasising trait measurement, however, researchers in this area may have created a circular argument, whereby we conceive of anhedonia as a trait simply because we measure it as such. It is, therefore, important for subsequent research to consider the test-retest stability of anhedonia. Finally, it may be that specific aspects of anhedonia are differentially impacted by the course of illnesses such as MDD. For example, Blanchard, Horan and Brown (2001) observed a decrease in self-reported social anhedonia in a one-year follow-up study of patients with MDD. This suggests these patients discovered a renewed interest in social interactions and interpersonal relationships. Thus, arguments exist for the further consideration of specific facets of anhedonia and how they may be affected during the progression of mental ill health (see section 1.9 for further discussion). Anhedonia also demonstrates a familial association (criterion e). As noted above, levels of anhedonia are elevated in first-degree relatives of people with depression relative to the general population (Liu et al., 2011; 2016) and relatives of patients with MDD show altered neural responses when processing rewards and punishments (McCabe, Woffindale, Harmer & Cowen, 2012). In contrast to this favourable evidence supporting the role of anhedonia as an endophenotype for depression, there is limited evidence to substantiate its specificity to MDD (criterion a). Anhedonia plays a core role in a range of other disorders, e.g. schizophrenia, Parkinson's Disease and addictive behaviours. This is a key area of overlap between the endophenotypic approach and the aims of the RDoC. For example, given the broad array of reward processing facets and of anhedonic deficits, considerable research has sought to establish specific patterns of reward processing deficits that are idiosyncratic to specific disorders, e.g. depression and bipolar disorder (see, e.g. Nusslock, Walden & Harmon-Jones, 2015). In contrast, a dearth of research has attempted to establish the cosegregation of anhedonia (criterion d; Pizzagalli, 2014).

Taken together, literature in both the RDoC and endophenotypic domains suggests that early conceptualisation of anhedonia as a basic deficit in reward liking or pleasure was misguided. The current consensus focuses on anhedonia as a range of impairments in anticipatory reward processes, including willingness to expend effort for reward. Such impairments seem to be trait-like in nature, likely reflecting broad individual differences in underlying neurobiological systems engaged in approach motivation. Conceptual approaches such as the RDoC and work on endophenotypes point to the need to consider individual differences in trait-like symptoms, such as anhedonia, and the importance of integrated theory and measurement spanning biological, psychometric and behavioural domains.

1.6 Reinforcement Sensitivity Theory

Reflecting the integral nature of motivational processes to behaviour, several theories emphasise the role of reward processing in personality (e.g. Depue & Collins, 1999; Gray & McNaughton, 2000). The reinforcement sensitivity theory (RST; Gray, 1972; Gray & McNaughton, 2000) is one such theory, which has been particularly influential in both the personality and clinical literatures. The original reinforcement sensitivity theory (oRST; Gray, 1970; 1982) and its revision (rRST; Gray & McNaughton, 2000) assert a biological basis for personality. This theory draws on three systems: the behavioural approach system (BAS), the fight-flight-freeze system (FFFS) and the behavioural inhibition system (BIS). According to the most recent iteration of the theory, the rRST (Gray & McNaughton, 2000), the BAS represents a general approach system toward rewarding stimuli, both conditioned and unconditioned. This system gives rise to the experience of 'anticipatory pleasure' (Corr, 2008) and facilitates approach behaviours designed to decrease the (physical, temporal or psychological) distance between the organism and the desired stimulus. The FFFS is an analogue to BAS in the punishment domain, which mediates the response to aversive stimuli, triggering avoidance and escape behaviours, i.e. withdrawal / avoidance motivation. Such behaviours are designed to increase the distance between the organism and the perceived threat and give rise to emotions pertaining to fear and avoidance. Finally, the BIS operates as a conflict resolution system, which strives for reconciliation when two goals are in competition. For example, in the case of win / lose gambles, BAS and FFFS may be in competition, as the individual decides between accepting or rejecting a bet

on which they stand to win or lose money. In this instance, the BIS is hypothesised to work to inhibit conflicting behaviours to achieve a resolution, culminating in behavioural approach or withdrawal. BIS is not limited to the resolution of approach / withdrawal conflicts, but also plays a role in balancing competition in BAS/BAS and FFFS/FFFS conflicts, e.g. regulating and directing behaviour when two rewards seem equally palatable. Thus, BIS may play an important role in deciding how much effort to expend in a choice of two rewards of varying magnitude and work requirement, e.g. as in Treadway et al.'s (2009) Effort Expenditure for Reward Task (EEfRT).

1.6.1 Anhedonia and the Behavioural Approach System (BAS)

There is clear conceptual overlap between anhedonia; a range of deficits primarily affecting motivation toward rewards, and lower activity in the behavioural approach system; a neurobiological system thought to regulate an organism's goal-motivated behaviour. Indeed, self-report and behavioural experiments suggest that decreased approach motivation and a lack of willingness to expend effort for reward are core aspects of anhedonia (Treadway et al., 2009; Treadway & Zald, 2011). An underactive BAS is thought to underlie decreased positive affect and motivation for reward (Davidson, 1992), which puts an individual at increased risk of developing depression (Fowles, 1988). The BAS is typically assessed using Carver and White's (1994) BIS / BAS scales; a self-report measure comprising items assessing behaviours thought to reflect core aspects of approach and withdrawal motivation (this questionnaire was developed to reflect the oRST, in which BIS was conceptualised as the system mediating withdrawal from threat, rather than conflict resolution). Using the BIS / BAS scales, these putative systems have been linked to depressive psychopathologies, including MDD and bipolar disorder. Specifically, high BIS and low BAS have been linked to depression (e.g. Kasch, Rottenberg, Arnow & Gotlib, 2002), whereas high BAS and low BIS have been associated with manic symptoms of bipolar disorder (e.g. Alloy et al., 2009). Indeed, similar to the presence of anhedonia, self-reported levels of (low) BAS, were found to predict a diagnosis of depression, as well as the severity and progression of that depressive illness over the course of six months (McFarland, Shankman, Tenke, Bruder & Klein, 2006). Thus, it appears that the BAS and anhedonia reflect conceptually overlapping systems that are similarly implicated in depression and are both sensitive to individual differences in approach motivation.

1.6.2 Difficulties with the BIS / BAS model

The rRST makes a number of hypotheses that differ from – or even contradict – the original theory. These are fully outlined and discussed elsewhere (see, e.g. Corr, 2008; Smillie, Pickering & Jackson, 2006), however, some of these are pertinent to the literature relevant to this thesis and will be emphasised here. The oRST asserted that the BIS and FFFS worked in parallel, so that BIS mediated the response to conditioned aversive stimulus and innate 'fear-inducing' stimuli, while FFFS was responsible for avoidant behaviour in the face of unconditioned threatening stimuli. As outlined in the preceding sections, BIS is no longer considered responsible for withdrawal / avoidance behaviour, per se, but rather, BIS is thought to reconcile conflicts when two goals are in competition. Despite this revised theoretical stance – and the introduction of several self-report measures reflecting the rRST (e.g. Corr & Cooper, 2016) - much of the literature derived from RST relies on the original conceptualisation of these approaches and is measured using Carver and White's (1994) BIS / BAS scales; a self-report measure derived from the oRST. This is particularly problematic in the literature on EEG frontal asymmetry (discussed below; see section 1.7.1), in which the traditional view of BAS as approach and BIS as withdrawal motivation continues to permeate research (e.g. see a recent review by Reznik & Allen, 2018).

Reflecting the multidimensional nature of reward processing and anhedonia outlined above, the BAS has more recently been conceptualised as a multi-faceted system, comprising several stages, which show considerable overlap with the spectrum of reward processing outlined in section 1.3. This view is summarised by Krupic and Corr (2017), who argue that conceptualising the BAS as a single system is an oversimplification of the construct, out of sync with much of the neurobiological research on the reward system and which may, in part, account for inconsistencies in the literature on RST. They point to a need to integrate the BAS with the literature on reward processing, but acknowledge that the multidimensional nature of both constructs, combined with a variety of measurement issues, make this integration problematic. Krupic and Corr (2017) argue for a four-part BAS system, made up of a wanting or capturing stage, reflecting a desire to possess resources; an incentive

motivation state, in which new resources are identified and sought; a striving stage, during which the organism invests effort in goal achievement; and, finally, a liking stage, in which the organism responds to the reward they have received. While this approach represents an advance on prior work and may help to disentangle certain complexities in reward processing, much of the nomenclature is adapted from prior work (e.g. Berridge & Robinson, 2003), but used in a different context, arguably lending greater confusion to the literature. Nonetheless, the core argument - the need to integrate these parallel literatures – is valid and is in keeping with the spirit in which this thesis has been conceived.

1.7 EEG frontal asymmetry

One such attempt to integrate the RST and neuroscientific approaches to personality and clinical psychology can be observed in the literature on EEG frontal asymmetry. Approach and withdrawal motivations are purportedly mirrored in the ratio between left and right activity at homologous electrodes in frontal neuroanatomical regions, using an electroencephalograph (EEG) recording. The alpha band (8-13Hz) of EEG activity has particularly been implicated in this regard (for reviews, see Coan & Allen, 2004; Reznik & Allen, 2018; Thibodeau, Jorgensen & Kim, 2006, though see also Wacker, Chavanon & Stemmler, 2010). Alpha activity is suggested to have an inhibitory effect on cortical activation, such that activity in the alpha band is inversely related to cortical activity (e.g. Laufs et al., 2003). Frontal asymmetry scores are usually assessed so that the alpha activity at left frontal electrodes is subtracted from homologous right frontal electrodes (typically F3 and F4, but variation exists; for discussions of methodological issues in frontal alpha asymmetry, see Coan & Allen, 2004; Smith, Reznik, Stewart & Allen, 2017*)*. This results in a difference score whereby greater left (relative to right) alpha asymmetry (indicating decreased left relative to right neural activity) is thought to reflect increased avoidance / withdrawal motivation. The converse is also true; less left (relative to right) alpha asymmetry (indicative of increased left relative to right neural activity), is thought to reflect increased approach motivation. Typically, greater left asymmetry is taken to reflect neural activity (rather than alpha power) and thus, greater approach motivation. Similarly, relatively greater right asymmetry should be interpreted as increased neural activation in the right hemisphere, thus indicating greater withdrawal motivation.

1.7.1 Frontal asymmetry and the approach / avoidance theory of motivation

It is beyond the scope of this introduction to provide a systematic review of the research linking EEG frontal asymmetry to approach and withdrawal behaviours, however, a brief summary of some relevant work and issues will be presented. First, some basic work establishing links between approach motivation and greater left (relative to right) frontal asymmetry will be presented. Second, the debate over trait versus situational influences on EEG alpha asymmetry will briefly be described and the argument for greater clarity in our conceptualisation of how frontal asymmetries relate to approach and withdrawal motivations will be presented. Finally, the relatively underspecified relationship between withdrawal motivation and relatively greater right (than left) alpha asymmetry will be introduced.

Davidson (1992) explicitly linked asymmetries in the left and right frontal regions to approach and withdrawal motivation, respectively. Dubbed the motivational direction model, this theory was based on three sources of evidence: First, the relative importance of the cerebral cortex in aspects of human emotional behaviour and the anatomical reciprocity of this area with subcortical and posterior cortical regions implicated in emotion, e.g. the limbic system (Luria, 1973). Second, an emerging body of neuropsychological evidence, which linked damage to the left frontal hemisphere with the presentation of depressive symptoms, including apathy, depressed mood, difficulty initiating behaviour and a loss of interest and pleasure in people and objects – behaviours broadly reflecting an anhedonic phenotype (e.g. Gianotti, 1969, 1972). A complementary, albeit smaller, body of evidence linked damage in right frontal areas with the expression of manic symptoms and a heightened response to fear-inducing stimuli, suggesting a role for the right hemisphere in mediating withdrawal behaviours. Such observations were enhanced by experimental evidence in which the left hemisphere was inactivated through the injection of intracarotid Amytal. Terzian and Ceccotto (1959) reported different emotional reactions in patients, depending on which hemisphere was inactivated: participants with an inactivated left hemisphere displayed a similar depressive response to those patients with left unilateral damage. In contrast, participants whose right hemisphere had been inactivated with Amytal, presented with

a manic euphoric reaction. These claims were supplemented by a series of EEG studies, linking regional hemispheric asymmetries to approach and withdrawal behaviour (e.g. Sutton & Davidson, 1997). These will be discussed in more detail in the following section. Third, and perhaps least convincingly, Davidson utilised observations of children, who tend to approach and reach for objects more frequently with their right hands in early development, irrespective of their later handedness (e.g. Young, Segalowitz, Misek, Alp & Boulet, 1983). These reaching and grasping behaviours are ostensibly linked to approach motivation, thus suggesting a left-hemisphere bias for approach motivation behaviours. Taken together, Davidson argued that these strands of evidence pointed to a unique role for the frontal cortex in emotional processing and a basis for a generalised lateralisation of emotion / motivation, in which approach for rewards was left-lateralised and withdrawal from punishment was right-lateralised. By extension, he argued that decreased activation of the left cerebral hemisphere (relative to that of the right) placed an individual at an increased risk for the development of depression (reflecting the catastrophic depressive reaction observed by Gianotti and others). Conversely, a relative deficit in right (compared to left) activation left the individual vulnerable to the development of anxiety disorders. Davidson argued that this vulnerability could best be observed in the alpha band of an EEG recording at frontal sites.

From the inception of this theory, a lack of clarity existed as to whether this frontal lateralisation reflected individual differences in *state* or *trait* approach / withdrawal motivation; a debate that continues to permeate the literature today (see, e.g., Coan & Allen, 2002), and the relationship between the right frontal cortex and withdrawal behaviour was grounded in less robust evidence that its left-hemisphere analogue (Davidson, 1992). The original Davidson theory suggests that anterior asymmetry is indicative of a propensity to behave in a more approach- or withdrawal-oriented manner in the presence of a stimulus which elicits a particular emotion. Davidson (1992) specifically states that *"in the absence of a specific elicitor, differences in affective symptomatology among individuals with different patterns of anterior activation asymmetry or asymmetry of anterior brain lesions would not be expected."* (p.129). Though he does acknowledge that baseline anterior asymmetries may be linked to individual differences in dispositional mood / emotional traits (Tomarken, Davidson, Wheeler & Doss, 1992). However, contemporary studies don't typically reflect this

interplay of state and trait effects on frontal EEG asymmetry and tend to emphasise trait-like aspects of resting state EEG.

Much of the work linking approach motivation to EEG asymmetry in the alpha band is based on correlations between Carver and White's (1994) BAS sub-scale and relatively greater left (than right) EEG asymmetry (e.g. De Pascalis, Cozzuto, Caprara & Alessandri, 2013; Hewig, Hagemann, Seifert, Naumann & Bartussek, 2006; Sutton & Davidson, 1997; see Harmon-Jones & Gable, 2017 for a recent review). In contrast, few studies have sought to link actual approach-related behaviour to relative left frontal asymmetry (see Hughes, Yates, Morton & Smillie, 2015 and Pizzagalli, Sherwood, Henriques & Davidson, 2005 for notable exceptions). However, controversy exists over the validity of the relationship between frontal asymmetry and BAS, e.g. Wacker, Chavanon and Stemmler (2010) failed to observe this association in four separate studies and reported no substantial relationship between BAS and frontal EEG asymmetry in the alpha band, based on a meta-analysis of work in this area.

Some researchers attribute these mixed findings to the influence of state effects on frontal asymmetry, in line with the aforementioned quote by Davidson (1992). Indeed, studies employing situational manipulations of positive and negative affect often report potential mediator effects on frontal asymmetry, e.g. individual differences in self-reported liking for desserts and time since last meal were related to variance in frontal asymmetries in response to viewing images of desserts and neutral stimuli, so that participants with higher liking of dessert and a longer duration since their last meal had greater relative left frontal asymmetry in response to images of dessert (relative to neutral) images (Gable & Harmon-Jones, 2008; Harmon-Jones & Gable, 2009). In contrast, the presentation of appetitive desserts on their own (i.e. without considering the influence of attitudes toward desert and time since last meal) had no main effect on frontal asymmetry. However, such situational influences tend to be broad-ranging and are often ambiguous (see, for example, Wacker, Mueller, Pizzagalli, Hennig & Stemmler, 2013, in which the motivational context was the presence of an experimenter, whose attractiveness was retrospectively judged by participants), undermining the ability to draw concrete conclusions about the role of situational factors in influencing EEG asymmetries. Furthermore, Hagemann, Hewig, Seifert, Naumann and Bartussek (2005) argue for a 60 / 40 model of frontal alpha asymmetry,

whereby 60 per cent of the variance in the asymmetry score reflects temporally stable, consistent trait effects, while the remaining 40 per cent of the variance is due to situational effects or interactions. In keeping with the trait-dominance of this variance, a recent review by Palmiero and Picardi (2017) argues that most of the work in this area supports the motivational direction theory of frontal asymmetry, though they also suggest that this model may be more complex than often thought.

Supporting this argument for a more nuanced interpretation of the relationship between frontal EEG asymmetry and approach motivation, many researchers have argued that more attention needs to be given to study design in this area, particularly the importance of distinguishing between frontal asymmetry as a moderator, mediator, predictor or outcome in these paradigms (see Reznik and Allen, 2018, for a recent review and discussion) to enhance theory-based research in this area. Placing specific emphasis on the rRST, Wacker, Chavanon, Leue and Stemmler (2008) argue for a more nuanced variant of the motivational direction model, which they term the behavioural activation – behavioural inhibition model of anterior asymmetry (BBMAA; Wacker, Heldmann & Stemmler, 2003). Briefly, this approach argues that goal-directed motivation – irrespective of whether it pertains to approach (i.e. BAS) or withdrawal (i.e. FFFS) – is related to left lateralised activation, whereas BIS-drive goal-conflict or BIS mediated inhibition of goal pursuit is linked to greater right (relative to left) frontal asymmetry. Supporting this model, they report a correlation between left anterior activation and withdrawal motivation, albeit during an imagery-induced manipulation of BIS / BAS / FFFS states.

In contrast to the plethora of work attempting to link left hemisphere asymmetry to approach motivation, the relationship between withdrawal motivation and frontal asymmetry is relatively underemphasised in the literature. As noted above, Wacker et al. (2008) observed a relationship between state-manipulated EEG asymmetry and the rRST conceptualisation of FFFS. In contrast, much of the literature in this area relies on the oRST and views withdrawal motivation as right-lateralised (e.g. Sutton & Davidson, 1997). As with the studies focusing on BAS, work considering the putative link between relative right asymmetry and withdrawal motivation, as assessed by the BIS subscale (note, Carver regards this subscale as reflective of punishment / threat

sensitivity; Carver, 2009) is not always clear cut, with several researchers failing to report an association (e.g. Amodio, Master, Yee & Taylor, 2008; Coan & Allen, 2003).

In contrast, the developmental literature shows reasonably robust results for the relationship between attachment and frontal EEG asymmetries to inhibited / avoidance behaviours when presented with novel or threatening stimuli (see Gander & Bucheim, 2015 for a review). Calkins, Fox and Marshall (1996) observed greater right (compared to left) frontal activation in 9 month olds, which was associated with more inhibited exploratory behaviour at 14 months in a group of infants classified as high negative affect, compared to their high positive affect peers. Similarly, Hane, Fox, Henderson and Marshall (2008) found that four-month-old infants prone to negative reactions were more likely to show avoidance behaviour and reduced approach behaviour in the face of a fearful stimulus at 9 months, which was accompanied by a pattern of greater cortical activation at right (relative to left) frontal regions. Extending this work, Buss, Schumacher, Solski, Kalin, Goldsmith & Davidson (2003) report a link between avoidant behaviours (fear and sadness), relative right asymmetry (indicative of greater right cortical activation) and higher levels of both basal and reactive cortisol in 6-month old infants in response to a negative affect task.

Taken together, this work illustrates a reliance on out-dated self-report measures of approach and withdrawal behaviours (e.g. Carver and White's (1994) BIS / BAS scales), which may, in part, explain discrepancies in the literature. Thus, there is a clear need to establish whether the motivational direction hypothesis of frontal asymmetry can be related to actual behavioural measures of approach and withdrawal motivation. The focus on broad constructs, e.g. the BAS, overlooks the more nuanced, multidimensional nature of reward processing (see Krupic & Corr, 2017 and section 1.3 above). By conflating disparate aspects of behavioural approach (and withdrawal), this literature risks masking significant effects, due to potential suppressor effects of discrete facets of this system (see Heym, Ferguson & Lawrence, 2008). Focusing on sub-components of reward processing is particularly important if we are to consider frontal EEG asymmetries as putative markers of psychopathology, per Davidson's (1992) argument that that decreased activation of the left cerebral hemisphere (relative to that of the right) places an individual at an increased risk for the development of depression (Nusslock, Walden & Harmon-Jones, 2015; Reznik & Allen, 2017). In light

of the emphasis placed on brain-behaviour relationships in psychopathology by new initiatives such as RDoC and the search for endophenotypes, it is particularly important to evaluate our measurement tools and ensure convergent validity across neuroimaging, behavioural and psychometric domains.

1.8 The neurobiological bases of reward processing

Evolutionary arguments indicate that approach and withdrawal motivation are fundamental to the existence of all organisms. Our ability to pursue rewarding stimuli, such as sex and food, and to avoid or withdraw from threats are essential survival mechanisms, tied to healthy psychological wellbeing. Reflecting the fundamental nature of these motivational processes, numerous studies have demonstrated that the discrete aspects of reward processing outlined above are linked to neurobiological substrates that are at least partly dissociable, in both animal and human models (Berridge & Kringelbach, 2008; Der-Avakian & Markou, 2012). This section will consider some of the key neurobiological processes underlying reward processing, emphasising dopaminergic mechanisms and their role in motivational processes and effort-cost decision-making (ECDM). A putative dopaminergic basis for the lateralisation of approach motivation and EEG asymmetry will also be outlined.

1.8.1 Dopaminergic mechanisms in the human brain

Neurobiological studies provide considerable support for the existence of discrete sub-components of reward processing. While various aspects of reward have been associated with a variety of brain regions, neural systems and neurotransmitters, dopamine (DA) and the dopaminergic reward pathways are most commonly implicated in reward-related behaviour. Three core pathways of dopaminergic projection have been identified and are illustrated in Figure 1.2. First, the nigrostriatal pathway (illustrated in purple), originates in the substantia nigra and projects primarily to the striatum (comprised of the putamen and the caudate nucleus). This pathway is strongly implicated in motor control and habit learning. Second, the mesolimbic pathway (illustrated in orange), originates in the ventral tegmental area (VTA) and terminates in the ventral striatum (particularly important are those terminals in the nucleus accumbens (NAcc)), the amygdala and the hippocampus. This pathway is implicated

in a variety of reward-related processes, including motivation, reinforcement and associative learning. Third, the mesocortical pathway (illustrated in yellow), which also originates in the VTA, projects to areas in the cortex. These areas include the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC) and the insula. Core functions associated with this pathway include the valuation of rewards, memory and inhibition.

Two types of dopaminergic transmission occur throughout these pathways: tonic and phasic transmission (Grace, 1991; Grace, Floresco, Goto & Lodge, 2007). Tonic dopaminergic function represents a steady or baseline state of DA in downstream structures, which facilitates the typical function of the neural pathways outlined above (Schultz, 2007). In contrast, phasic DA transmission occurs when a sharp increase or decrease in DA firing is observed in response to a stimulus, resulting in an increase in extracellular dopamine at target sites. This response continues for approximately 100-500 milliseconds and provokes a change in the concentration of dopamine in downstream structures, which lasts for several seconds (Bromberg-Martin, Matsumoto & Hikosaka, 2010; Schultz, 2007). Phasic transmission occurs in response to different kinds of rewards and reward-related cues (Schultz, 2007) so that a reward that exceeds expectations (i.e. that is better than originally predicted) elicits a phasic activation of dopamine transmission, dubbed a positive prediction error (Enomoto et al., 2011; Shultz, 2013). In contrast, when a reward fails to live up to expectations (i.e. is worse than originally predicted), a depression in dopaminergic firing is observed, called a negative prediction error). Finally, a reward that maps exactly on to the predicted value elicits no phasic response (Enomoto et al., 2011; Shultz, 2013). Such reward prediction error (RPE) responses are thought to reflect dopamine-mediated reward learning. Five classes of DA receptor exist: D_1, D_2, D_3, D_4 and D_5. These receptors are typically grouped into two 'families': D_1-like receptors (comprising D_1 and D_5) and D_2-like receptors (comprising D_2, D_3 and D_4). Activity of D_2-like receptors is most closely linked to tonic dopaminergic transmission, whereas D_1-like receptors tend to be stimulated by the phasic dopamine response (Goto, Otani & Grace, 2007).

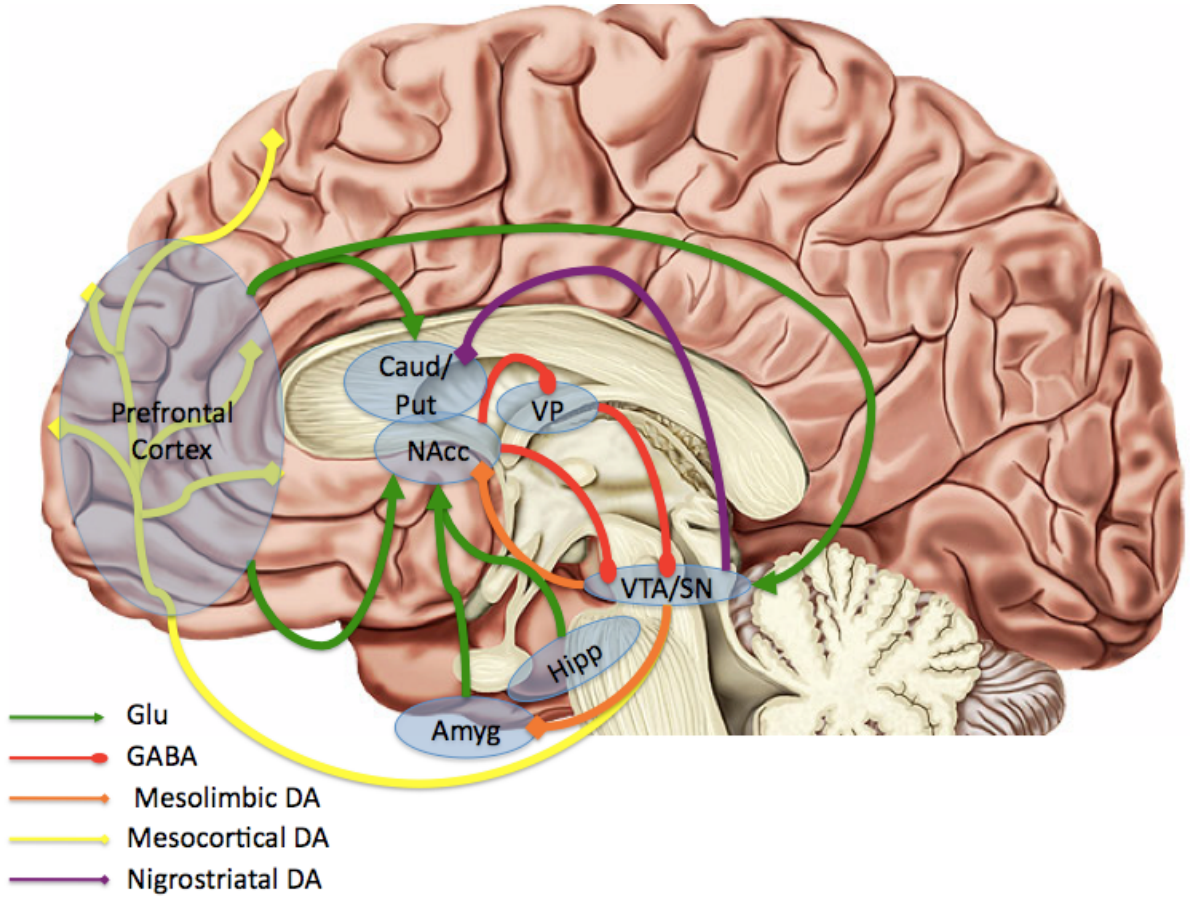

Figure 1.2: Dopaminergic projections in the human brain, adapted from Treadway (2011). The orange lines outline the mesolimbic dopaminergic pathway, which originates in the ventral tegmental area (VTA) / substantia nigra (SN) and projects to the Nucleus Accumbens (NAcc) and the Amygdala (Amyg). The yellow lines delineate the mesocortical dopamine pathway, which begins in the VTA / SN and projects to areas in the Prefrontal Cortex. The purple line follows the nigrostriatal dopaminergic pathway, which projects from the VTA / SN to the Caudate (Caud) and the Putamen (Put).

1.8.2 The role of dopamine in reward processing

1.8.2.1. Dopamine and reward liking

The role of dopamine in reward processing has been hotly debated for several years. Four primary theories have been set forth, implicating dopamine in the experience of hedonic value (e.g. Wise, 1980; 1985), as a teaching signal, responsible for reward learning (e.g. Schultz 2007; outlined above), as the driver of incentive salience (e.g. Berridge & Robinson, 1998) and in mediating work-related response costs (e.g.

Salamone & Correa, 2012). This section will focus on dopaminergic mechanisms in approach behaviour, arguing for a specific role for dopaminergic processes in the ECDM associated with reward approach.

Early hypotheses, such as that of Wise (1980; 1985), proposed that dopamine was the "pleasure" neurotransmitter, which played a crucial role in the subjective pleasure associated with a given reward. This theory clearly implicates DA function in the liking phase of reward, however, it has garnered little empirical support. Crucially, lesioning NAcc dopamine synapses does not impair hedonic tone ('liking' responses) in rats (Berridge & Robinson, 1998). Similarly, administration of neuroleptic drugs, which work to block D_2 receptors, dampening the levels of dopamine released at these sites, does not affect rats' liking of palatable ethanol-infused water (Kaczmarek & Kiefer, 2000). Indeed, when mice are selectively bred to be incapable of naturally synthesising DA, cessation of daily administration of levodopa (a drug to compensate for this natural deficiency), leads to near complete depletion of dopamine in the brain. Despite this almost total absence of dopamine, these mice continue to demonstrate a preference for sweet-tasting sucrose-infused water (compared to plain water), clearly showing intact liking. This preference for sweet-taste is independent of the relative calorie level of the water, as the DA-deficient mice also show a preference for a non-calorific sweetener, saccharin, over plain water (Cannon & Palmiter, 2003). Finally, further work has illustrated that increasing DA levels has no effect on liking behaviour. Genetically modified mice with up to 70 per cent higher levels of extracellular dopamine do not show altered liking responses in response to sweet tastes when their orofacial responses are compared to those of DA-intact mice (Peciña, Cagniard, Berridge, Aldridge & Zhuang, 2003).

1.8.2.2 Dopamine and motivation for rewards

In contrast, these hyperdopaminergic mice show marked changes in reward motivation behaviours (Peciña et al., 2003). Relative to control mice, mice genetically modified to have higher levels of extracellular dopamine by 'knocking out' the dopamine transporter gene (DAT), show higher reward wanting (greater incentive motivation), and, possibly, enhanced reward learning. These hyperdopaminergic mice learned a runway task after fewer trials, resisted distractions better to obtain a reward, and

proceeded more directly to the reward, relative to control mice. Peciña and colleagues (2003) argue that these behaviours reflect greater incentive salience ("wanting") of rewards on the runway task. This interpretation of the results reflects the incentive salience theory mentioned above, which implicates dopamine in the approach or anticipatory phase of reward processing. According to Berridge and Robinson (1998), dopamine is involved in the incentive salience of reward processing, i.e. motivation (according to this theory, motivation can be either conscious or unconscious) which promotes approach toward a reward (and, if applicable, the subsequent consumption of that reward) and mediates the organisms' wanting (but not liking) of rewards. Thus, this hypothesis suggests that liking and wanting are two dissociable processes, mediated by different neural systems. Based on the work by Peciña et al. (2003), this dissociation of liking and wanting behaviours seems somewhat plausible. Accumbens dopamine, according to this hypothesis, transforms the representation of a conditioned stimulus to make it seem attractive and desirable. This is accompanied by a motivational aspect, in which the reward is worth pursuing. According to this hypothesis, the motivational aspects of the reward can be stripped away, leaving the hedonic aspect of the reward intact, but removing the goal-directed willingness to work for the reward. As outlined in the preceding paragraph, it is possible to almost completely deplete an organism's DA levels without affecting their liking response (e.g. Cannon & Palmiter, 2003). This reward wanting hypothesis differentiates between conscious reward wanting, which is linked to goal-directed behaviours and unconscious wanting of rewards, which may not be directly accessible to our conscious experience (Kringelbach & Berridge, 2010).

In keeping with the incentive salience hypothesis, attempts have been made to establish whether anhedonic deficits can be considered motivational (pertaining to reward wanting) or consummatory (reflecting reward liking) in nature. Patients with depression and schizophrenia, both characterised by anhedonia, show similar responses to controls on a human analogue of the sweet taste test (Berlin et al., 1998; Dichter et al., 2010), indicating intact reward liking. In contrast, a variety of motivational and learning-related deficits have been observed in patients with these disorders, spanning reduced willingness to expend effort for reward, blunted reinforcement learning, impairments in effort-cost decision making, and failure to acquire a preference for reward-biased

stimuli (for a summary and discussion of the dominant findings in this literature, see Pizzagalli, 2014).

1.8.2.3 Dopaminergic mechanisms in effort expenditure for reward

A recent trend in this literature has been to emphasise deficits in effortful behaviour (also called behavioural activation). This concept extends beyond the incentive / cognitive salience model summarised by Berridge and Robinson (2003) and argues that the mesolimbic dopaminergic system plays a specific role in effort-cost decision making (ECDM). Much of the work in this area emerges from paradigms in which rats are presented with two alternate feeding options: a freely available, but not particularly tasty, lab chow (low effort, low reward) or a very palatable alternative that they must exert physical effort to obtain, e.g. by pressing a lever (high effort, high reward). Healthy rats show a strong preference for the high effort, high reward (HE/HR) alternative 90 per cent of the time, however, when DA is attenuated (e.g. through administration of 6-hydroxy DA lesions, which lead to a local blockade of DA), this preference is reversed and rats opt for the low effort, low reward (LE/LR) option (Cousins & Salamone, 1994; Salamone, Correa, Farrar & Mingote, 2007). Crucially, this altered preference is independent of other changes in appetite, food preference, calorie level or locomotor ability (Correa, Carlson, Wisniecki & Salamone, 2002; Cousins, Sokolowski & Salamone, 1993; Salamone, Koychev, Correa & McGuire, 2015). In contrast, enhancement of dopamine with D-amphetamine (specifically when acting on D_1 and D_2 receptors), increases rats' willingness to expend physical effort to obtain palatable rewards (Bardgett, Depenbrock, Downs, Points & Green, 2009). The effects of dopaminergic manipulation also seem to be specific to ECDM, as rats with depletion of up to 99 per cent of the dopamine neurons in the NAcc and the neostriatum show normal intact hedonic responses to sucrose-infused water (compared to quinine), suggesting a preserved "liking" response (Cannon & Palmiter, 2003). Taken together, this evidence suggests that merely stating that dopamine depletion impairs motivation for reward generally is an over simplification, rather there is a selective role for dopamine in the willingness to expend effort in pursuit of rewards.

1.8.2.4 Dopaminergic mechanisms in withdrawal motivation

In addition to its core role in approach motivated behaviour, dopamine is also posited to transmit signals related to aversive stimuli, prompting withdrawal motivation (Salamone & Correa, 2012; Salamone et al., 1997). Bromberg-Martin, Matsumoto and Hikosaka (2010) argue that the dopaminergic system comprises several sub-types of dopamine neuron, including a sub-group of neurons sensitive to motivational value. This population of neurons is excited by rewarding events and inhibited by aversive events. In turn, these neurons support brain systems engaged in goal-seeking behaviour and other aspects of reward processing. A second sub-group of dopaminergic neurons encode motivational salience – both rewarding and aversive. This sub-group of neurons support neural systems underpinning motivational drive and cognitive processing. Bromberg-Martin and colleagues argue that these systems work together to coordinate downstream neural structures and motivated behaviour, hence incorporating a role for dopamine in mediating both approach and withdrawal behaviours. Salamone and Correa (2012) argue that NAcc dopamine and, particularly tonic dopamine transmission, is central to mediating both incentive salience and motivation value processes.

In keeping with this role for dopamine in withdrawal motivated behaviours, a substantial body of literature implicates dopaminergic processing in response to aversive and stressful experiences, including rodent paradigms, such as foot shock, restraint, social stress, e.g. overcrowding, social defeat. Such procedures have been linked to increased release of dopamine via microdialysis (e.g. McCullough, Sokolowski & Salamone, 1993; Salamone, Cousins & Bucher, 1994; Young, 2004). Microdialysis captures changes in levels of extracellular dopamine over a longer timescale and is thus thought to reflect changes in tonic dopamine levels. Though more recent work suggests that dopaminergic pathways are differentially affected, depending on the nature of the stressor, as well as characteristics of the organism (e.g. Cuadra, Zurita, Lacerra, & Molina, 1999) and that stress may have discrete influences on different aspects of reward processing (see section 1.10).

1.8.2.5 The dopaminergic basis for lateralisation of motivation and frontal EEG asymmetries

Asymmetries are evident in the dopaminergic system and these have been linked to individual differences in stress reactivity and drug sensitivity in rodents, ostensibly threat- and reward- sensitive behaviours respectively (Carlson & Glick, 1989). Parkinson's Disease is a neurological disorder, characterised by the degeneration of dopamine cells in the substantia nigra, resulting in dramatically lower levels of dopamine in areas such as the putamen (Bjorklund & Dunnett, 2007). In the majority of patients, this degeneration is asymmetric and can be observed in the imbalanced deterioration of motor skills (Elbaz et al., 2005; Kempster, Gibb, Stern & Lees, 1989). Working with an un-medicated group of patients with a greater left-hemisphere deficit in dopamine, Maril, Hassin-Baer, Cohen and Tomer (2013) observed that participants minimised losses better than they maximised gains on a card-based gain-loss sensitivity task analogous to the Iowa Gambling Task (Bechara, Damasio, Damasio & Anderson, 1994). In contrast, patients with a greater right-hemisphere dopamine deficit demonstrated the opposite pattern on the card task. Thus, left-hemispheric deficits in dopamine were associated with decreased approach motivation, whereas relatively greater dopaminergic impairment in the right hemisphere was linked to impaired withdrawal motivation. The authors argue that this pattern of reward-related behaviour is in-keeping with Davidson's (1992) motivation direction hypothesis and provides support for the role of dopamine asymmetries in determining these motivational directions.

Building on this work, Tomer et al. (2014) observed that both self-reported motivation bias (assessed using the BIS / BAS scales) and a behavioural task assessing relative sensitivity to positive and negative feedback (the reward vs. punishment learning task; Bodi et al., 2009) in healthy participants was predicted by asymmetries in in D_2 receptor binding in frontal and striatal regions, assessed via Positron Emission Tomography (PET). Supporting this observation, Treadway et al. (2012b) reported an association between individual variation in D_2 and D_3 receptor sensitivity (in response to a *d* amphetamine challenge) in the bilateral ventromedial prefrontal cortex (vmPFC), left ventrolateral prefrontal cortex (vlPFC), left caudate and left inferior temporal gyrus and willingness to choose the hard task on the EEfRT (Treadway et al., 2009). Greater

receptor density in these areas was related to an increased willingness to expend effort for reward, especially when reward receipt was relatively unlikely (12 per cent). Porat, Hassin-Baer, Cohen, Markus and Tomer (2013) observed a similar lateralisation of effort in a group of un-medicated participants with Parkinson's related asymmetric deficits in dopamine. Mirroring the work of Maril et al. (2013), Porat and colleagues observed that patients with a greater left hemisphere deficit in DA showed diminished willingness to expend effort to increase financial gain (relative to decreasing financial loss) on a gain / loss progressive ratio task, in which effort was quantified by the number of button presses. In contrast, participants with greater right-hemisphere depletion of dopamine showed a reduction in effort to avoid minimising loss (relative to increasing gain). Notably, these findings were not due to significant between-group differences on motor deficits and performance patterns were reversed when patients were medicated with L-Dopa/ Carbidopa combinations, i.e. drugs that go some way to restore concentrations of dopamine in neural regions in which these have been depleted due to Parkinson's Disease. Taking medication that enhanced dopaminergic function led to an increased willingness to expend effort (though this increase was not statistically significant). Change scores, calculated to compare patients' performance on and off medication, indicated that those patients with greater right hemisphere reductions in dopamine were less willing to expend effort to maximise gains, but more willing to expend effort to minimise losses, when on medication. This represents a double dissociation when compared to their un-medicated performance. A similar dissociation was observed for patients with left hemispheric deficits, so that, when medicated, these patients showed greater effort to maximise gains, but less effort to minimise losses. This study presents potentially compelling evidence that dopamine-related functions in the left hemisphere are particularly implicated in approach motivation for rewards, while the right hemisphere characterises a similar pattern of activity for withdrawal motivation from threats, but the results should be interpreted with caution, as they are based on a small sample (N = 39) of patients with idiopathic Parkinson's Disease. Clearly, further work is needed to replicate these findings in larger samples.

The body of research providing direct evidence linking EEG frontal asymmetry to midbrain dopaminergic pathways is small, but compelling. Wacker, Müller, Pizzagalli, Hennig & Stemmler (2013) observed an association between relatively greater LFA and trait BAS (assessed via Carver & White's (1994) BIS / BAS scales) in an approach-

motivated context, however, this relationship was reversed for a group of participants who had received a dopamine D_2 blocker. This finding was conceptually replicated by Wacker (2018). Wacker et al. (2013) also reported an association between LFA and variation in the COMT Val158Met gene. The COMT Val158Met polymorphism is responsible for regulating catabolism of catecholamines, including dopamine, in the PFC and thus provides a link between LFA and dopaminergic processes. Wacker et al. (2013) report the relationship between LFA and the Val allele was positive for those participants interacting with an attractive experimenter (i.e. who were in an approach motivated state). In contrast, Katz, Sarapas, Bishop, Patel and Shankman (2015) report an association between LFA and the Met allele of COMT Val158Met. Katz et al. (2015) argue that frontal asymmetry mediates the relationship between COMT Met and consummatory pleasure (assessed by the TEPS; Gard, Gard, Kring & John, 2006). Thus, the nature of this relationship requires further clarification.

This body of work is clearly in need of further development, but this research tentatively suggests a role for the lateralisation of dopaminergic processes – particularly those related to the asymmetric density of D_2 like receptors (e.g. Tomer et al., 2014; Treadway et al., 2012) – in the approach or wanting stage of reward processing. It seems possible that this activity is particularly important in determining willingness to expend effort for rewards. D_2 like receptors predominantly reflect tonic dopaminergic transmission (Goto, Otani & Grace, 2007). Such transmission travels from mid-brain structures via the mesocortical dopaminergic pathway (see Figure 1.2) to frontal subcortical projection areas. While this mechanistic account requires further investigation and substantiation, it may be feasible that frontal EEG asymmetries assessed at resting state reflect asymmetric patterns of tonic dopamine activation in frontal regions, contributing to approach or withdrawal motivated behaviours, depending on the balance or sensitivity of dopaminergic receptors (Porat et al., 2013).

1.9 Issues with self-report measures of anhedonia

In contrast to the preclinical literature, which emphasises behavioural and neural aspects of reward processing deficits, anhedonia in humans is typically assessed using self-report questionnaire measures. In the personality domain, many of these are derived from Gray's (1972) theory of the behavioural approach and inhibition systems,

e.g. BIS / BAS Scales (Carver & White, 1994) and assess broad domains of motivational valance. In contrast, the clinically aligned literature has focused on measurement of anhedonia specifically rather than reward processing more generally. Multiple diverging measures have been created in an attempt to assess deficits in anhedonia and its component processes. Table 1.2 presents a summary of some of the most common self-report questionnaires, their relevant subscales and a brief description.

Traditionally, much of the anhedonia-specific measures have focused on consummatory aspects of reward processing. While this content reflects early conceptualisations of anhedonia (e.g. Ribot, 1896; Meehl, 1962; Wise, 1980), it is not in keeping with current understandings of anhedonia comprising primarily of motivational deficits in reward processing (see section 1.4). Though, of course, the validity of self-report as an assessment of consummatory pleasure is questionable, as such measures implicitly require the participant to imagine how they would / will feel in a given circumstance and thus may not accurately assess "liking" responses (Klein, 1987). Despite this issue, most "first generation" self-report measures of anhedonia primarily assessed pleasure or liking in response to rewards, e.g. the Fawcett-Clark Pleasure Scale (FCPS; Fawcett, Clark, Scheftner & Gibbons, 1983), the Chapman Physical and Social Anhedonia Scales (Chapman, Chapman & Raulin, 1976; Eckblad, Chapman, Chapman & Mishlove, 1982) and the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith, Hamilton, Morley, Humayan, Hargreaves & Trigwell, 1995). Such measures continue to permeate the literature today (see Rizvi, Pizzagalli, Sproule & Kennedy, 2016 for a recent review), despite being out of sync with the pre-clinical, clinical and neurobiological literature discussed above.

Reflecting this discrepancy between the conceptualisation of anhedonic deficits and the content of self-report measures of anhedonia, there have been inconsistencies in how these measures relate to behavioural assessments of reward processing. For example, higher scores on both the Chapman anhedonia scales (indicative of higher levels of anhedonia) were significantly related to reduced willingness to choose the hard task on the EEfRT, whereas scores on the SHAPS were unrelated to EEfRT performance (Treadway et al., 2009), suggesting discrepancies in the dimensions of consummatory pleasure assessed by these measures. A further difficulty is that these scales were

originally developed for use in specific populations. The Chapman scales were designed to assess anhedonic deficits in patients with schizophrenia, whereas the FCPS was developed for use with patients with depression. Reflecting these disparate contexts, the Chapman scales yield strong associations with non-affective personality aspects and symptoms of psychotic disorders, whereas the FCPS correlates moderately with measures of depression (Leventhal, Chasson, Tapia, Miller & Petit, 2006), again suggesting that these scales are measuring slightly different constructs.

Table 1.2 A representative selection of self-report measures of reward processes and anhedonia

Measure	Factors / subscales	Reference	Description
Chapman Anhedonia Scales	Physical and Social	(Chapman et al., 1976)	Trait measure assessing the enjoyment of various physical and social rewards. Originally developed to assess anhedonia in schizophrenia, but now used in a variety of samples.
Fawcett-Clark Pleasure Scale (FCPS)	Consummatory	(Fawcett et al., 1983)	Trait measure tapping consummatory enjoyment of everyday experiences. Developed to assess anhedonic depression.
Snaith-Hamilton Pleasure Scale (SHAPS)	Consummatory	(Snaith et al., 1995)	State-based measure assessing enjoyment of everyday pleasurable activities.
Temporal Experience of Pleasure Scale (TEPS)	Anticipatory and Consummatory	(Gard et al., 2006)	Trait measure, which attempts to dissociate anticipatory and consummatory pleasure.
Apathy Motivation Index (AMI)	Social; behavioural; emotional	(Ang et al., 2017)	Conceived as a measure of apathy sensitive to individual differences and a multi-dimensional representation of the construct.
Mood and Anxiety Symptom Questionnaire (MASQ)	Anhedonic-depression	(Watson et al., 1995)	Assesses low interest and pleasure and low positive affect. Developed to distinguish depressive symptoms from general distress and anxiety.
Anticipatory & Consummatory Interpersonal Pleasure Scale	Three factors: Intimate Social Interactions; Group Social Interactions; Social Bonding & Making Connections	(Gooding et al., 2014)	Developed to assess anhedonic deficits in the social domain.
Specific Loss of Interest and Pleasure Scale (SLIPS)	Single factor: recent changes in socially hedonic experiences	(Winer et al., 2014)	Assessment of recent change in enjoyment and interest. Ostensibly, a broad measure, but factor analysis indicates a single, primarily social factor.

Dimensional Anhedonia Rating Scale (DARS)	Pastimes / hobbies; foods / drinks; social activities; sensory experiences	(Rizvi et al., 2015)	Developed to assess a more multidimensional view of anhedonia, encompassing person-specific pleasure-giving examples of hobbies, food etc.
BAS Scale	Fun Seeking, Drive, Reward Responsiveness	(Carver & White 1994)	Developed with the Behavioural Inhibition Scale to operationalize Gray's Reinforcement Sensitivity Theory.
Sensitivity to Reward Questionnaire		(Torrubia et al., 2001)	Operationalization of Gray's Reinforcement Sensitivity Theory with an emphasis on responses to specific reward cues.
Appetitive Motivation Scale		(Jackson & Smillie 2004)	Operationalization of Gray's Reinforcement Sensitivity Theory with an emphasis on motivation to approach ideas and physical stimuli, and appraisal of obtaining rewards.

Adapted from Zald and Treadway (2017) and extended to encompass related measures.

Discrepancies between first generation self-report measures of anhedonia and task-based assessments likely reflect the relative specificity of the latter and the comparatively broad (and possibly misaligned) content of the former. As recognition of the heterogeneity of anhedonia has grown, several "second generation" self-report measures have emerged, attempting either to parse sub-components of anhedonic deficits or to hone in on specific domains of hedonic experience. One of the most promising questionnaires attempting to parse aspects of anhedonia is the Temporal Experience of Pleasure Scale (TEPS; Gard, Germans Gard, Kring & John, 2006). This scale was designed to be sensitive to the distinction between aspects of anticipatory ("wanting") and consummatory ("liking") pleasure and shows some merit as a measure of anhedonia, sensitive to individual differences in healthy participants (e.g. Gard et al., 2006), as well as in participants with sub-syndromal depression (Chentsova-Dutton & Hanley, 2010) and patients with schizophrenia (Gard, Kring, Germans Gard, Horan & Green, 2007). However, this questionnaire has primarily been used in groups with schizophrenia, limiting its ability to index anhedonia as a marker of depression. Finally, the factor structure of the TEPS has been questioned (see Ho, Cooper, Hall & Smillie, 2015), undermining the reliability of the dissociation between reward wanting and liking.

A two-factor structure, though an improvement on first-generation self-report measures, is arguably still insufficiently nuanced to pick up individual differences in anhedonia, such as those observed in neuroimaging and behavioural paradigms (see McCabe, 2018 for a discussion). Apathy is an umbrella term for a syndrome of motivational impairments, characterised by reductions in self-initiated goal-directed behaviour (Marin, 1991), which demonstrates considerable overlap with anhedonia, sharing underlying mechanisms and presenting similar clinical phenotypes (for a review and discussion, see Husain & Roiser, 2018). Efforts to parse apathy have taken a more nuanced approach compared to those examining anhedonia. The introduction of a new self-report measure, the Apathy Motivation Index (AMI; Ang, Lockwood, Apps, Muhammed & Husain, 2017) recognises individual differences in motivational impairments across cognitive, affective and behavioural domains. Using the AMI, Ang et al. (2018) report motivational impairments in behavioural and social – but not emotional – domains in a sample of patients with Parkinson's disease. These behavioural and social impairments were, in turn, linked to relatively greater levels of

anhedonia (assessed via the SHAPS) and depression (measured using the Geriatric Depression Scale, GDS-15; Yesavage & Sheikh, 1986), whereas emotional apathy was independent of these measures. These findings suggest two important implications: 1) psychiatric and neural disorders, such as Parkinson's disease and depression, may be liked to unique patterns of motivational deficits; 2) by focusing on broad dimensions of anhedonia, most currently available self-report measures will be insufficiently sensitive to detect these patterns. These implications are in keeping with the RDoC initiative (see section 1.5), which holds that current, broad diagnostic patterns mask important mechanisms unique to specific disorders and pushes for a new classification system, which focuses on basic brain-behaviour relationships and the integration of neural, behaviour, genetic and self-report measures of the core mechanisms implicated in psychopathology.

The need for more nuanced assessment of domains of anhedonia has received some attention in the psychometric literature. Rather than establishing a single scale, which reflects the multi-dimensional nature of the disorder, however, this work has sought to establish increasingly nuanced measures of sub-domains of anhedonia. One such example, the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS; Gooding & Pflum, 2014), focuses on pleasure deficits in the social domain. Similarly, the Specific Loss of Interest and Pleasure Scale (SLIPS; Winer, Veilleux & Ginger, 2014) assess recent changes in anhedonia over a two-week period, using a one-factor solution, primarily focusing on socially rewarding experiences. This trend toward development of increasingly nuanced measures is problematic for several reasons. First, it overlooks other potentially important aspects of anhedonic experience, e.g. these socially orientated measures exclude putative deficits in behavioural and emotional domains of motivated behaviour, such as those identified by the AMI (Ang et al., 2017; 2018). Second, the accumulation of multiple factors related to anhedonia, spanning temporal (e.g. anticipatory versus consummatory) and domain-specific (e.g. social, physical, behavioural or emotional) aspects of anhedonic deficits complicates the literature and blurs the measurement of anhedonic deficits. It also promotes the inclusion of multiple questionnaire measures (to encompass these different domains of anhedonia), putting researchers at increased risk of p hacking and necessitating much larger samples to ensure adequate power after correction for multiple comparisons. Supporting this observation, it is increasingly common for studies to incorporate

several measures of anhedonia, without providing a clear rationale for why these conceptually different measures are included (e.g. Rzepa, Fisk & McCabe, 2017; Yang et al., 2014).

A notable exception to the measures discussed above is the recently developed Dimensional Anhedonia Rating Scale (DARS; Rizvi, Quilty, Sproule, Cyriac, Bagby & Kennedy, 2015). The DARS is sensitive to anhedonic deficits across four domains: hobbies, food / drink, social activities and sensory experiences. Items were generated by the author and reviewed by five clinical psychologists. Although this lexical approach is a common method of generating questionnaire items (see also Ang et al., 2017), it is arguably subject to research and clinical biases. The DARS has been validated in both a community sample and a sample with MDD (Rizvi et al., 2015), however the factor structure of the measure remains to be confirmed and a dearth of research has sought to validate or otherwise adopt the measure in the literature (though a large-scale clinical trial currently running under the direction of Lam et al. (2016) and which aims to integrate biomarkers of antidepressant response, has adopted the DARS as a measure of anhedonia). Finally, although the DARS attempts to parse anhedonia, the factor structure of this questionnaire maps several experiential domains, i.e. social, hobbies, food / drink and sensory experiences, rather than reflecting the core aspects of reward processing outlined in section 1.3, e.g. anticipatory, effort expenditure, consummatory pleasure. Nonetheless, the DARS represents a step forward for the refinement of self-report measurement of anhedonia and underscores the importance of developing a broad questionnaire measure of anhedonia, sensitive to a range of putative deficits, and validating it with discrete neural and behavioural measures of reward processing.

1.10 Causal mechanisms underlying anhedonia and depression

Reflecting the push from initiatives such as the RDoC and the search for endophenotypes and biomarkers of psychopathology, attempts have been made to provide an integrated account of sub-types of heterogeneous disorders, such as MDD. Such efforts are characterised by an attempt to map the course of psychopathology from putative casual factors, via biological mechanisms of action, through to the presentation of clinical phenotypes. A variety of causes have been posited to explain depression and

it is likely that explanations for this disorder are multifactorial and complex. One putative causal factor, which has received considerable attention is the role of stress. Specifically, stress may promote the onset of depressive psychopathology by disrupting an organism's reward processing mechanisms. Stress is a well-acknowledged precursor and maintenance factor for depression, with recent work suggesting approximately 80 per cent of major depressive episodes (MDEs) are preceded by a major life event (Monroe, Slavich & Georfiades, 2014; Pizzagalli, 2014). Stress contributes to the maintenance of depression by increasing the likelihood of relapse (Lethbridge & Allen, 2008), the worsening of symptoms (Leskela et al., 2006), as well as being related to greater resistance to treatment (Amital et al., 2008). Particularly relevant is an individual's perceived stress, or stressors over which the individual feels they have little control, are unable to escape or avoid, or which they feel leads to a lowering of their status (Pizzagalli, 2014). This section will briefly highlight the relationship between stress and anhedonia, as well as a putative mechanistic account through which stress-induced inflammation may play a causal role in the development of anhedonia.

Pizzagalli (2014) provides a compelling case for the role of stress in the development of anhedonic depression. He argues that stress impacts negatively on mesocortical and mesolimbic dopaminergic pathways, leading to the deficits in incentive motivation and reinforcement learning that characterise anhedonia in MDD. This relationship is complex, not least because, dependent of the nature of the stressor, various aspects of reward processing may be differentially affected. Acute stress, for example, increases incentive motivation, however, chronic stress – particularly when perceived to be beyond the organism's control – leads to a reversal of this effect, triggering aversive or withdrawal motivation (Lemos et al., 2012). This observation is linked to the activity of the Corticotrophin releasing factor (CRF), a neuropeptide, which is released in response to acute stressors. The CRF acts on the NAcc to promote the release of dopamine (via the CRF receptors: CRF1 and CRF2). Chronic stress extinguishes this effect and subsequent recovery of the CRF activity is slow. This, in turn, triggers the switch from heightened approach motivation to increased withdrawal motivation (Lemos et al., 2012). Behaviourally, this attenuation of mesolimbic dopaminergic function is linked to a depressive phenotype, characterised by despair and a failure to cope in rodents (Cabib & Puglisi-Allegra, 2012).

The mesocortical and mesolimbic pathways respond in opposite manners when animals are presented with chronic, uncontrollable stressors. As noted above, chronic stress inhibits dopaminergic release in the NAcc (Cabib & Puglisi-Allegra, 2012). In contrast, severe, sustained, uncontrollable stress promotes dopaminergic activity in the medial PFC (mPFC) relative to an escapable stressor of similar intensity and duration (Cuadra, Zurita, Lacerra, & Molina, 1999). Dopamine inhibits activity in the mPFC, thus, increased dopaminergic function in this region may reduce mPFC-mediated behaviour, such as the activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis (Maier, Amat, Baratta, Paul, & Watkins, 2006). The HPA-axis plays a key role in mediating an organism's response to stress, as well as in regulating the immune system.

Such observations have led some researchers to articulate a causal role for stress-induced inflammation in the pathophysiology of depression (see reviews by Miller, Maletic & Raison, 2009; Felger & Treadway, 2017). The body's inflammation response is, in part, modulated by proteins called cytokines. Cytokines may worsen disease, i.e. pro-inflammatory cytokines, such as Interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF), or may work to promote healing, thus reducing disease; anti-inflammatory cytokines, i.e. IL-4, IL-10 (Dinarello, 2000; Opal & DePalo, 2000). Cytokines can also influence neural systems via links with neurotransmitters, including dopamine, serotonin and glutamate (Felger & Lotrich, 2013). Acute activation of inflammatory cytokines promotes adaptive behavioural and immune system responses, e.g. lethargy, to conserve energy and promote healing. However, chronic exposure to inflammatory cytokines, accompanied by persistent changes in neurotransmitter systems, can result in presentation of depression and other neuropsychiatric disorders (Felger & Lotrich, 2013). Peripheral markers of inflammation, such as pro-inflammatory cytokines; IL-6, tumour necrosis factor α (TNF-α), and elevated C-reactive protein (CRP), are frequently observed at increased rates in patients with depression (Dowlati, Hermann, Swardfager, Liu, Sham, Reim & Lanctot, 2010; Haapakoski, Mathieu, Ebmeier, Alenius & Kivmaeki, 2015; Zorilla et al., 2001). Stress has been causally linked to increases in these inflammatory markers, such as IL-6. For example, adolescents with a history of childhood adversity have elevated levels of IL-6, which was shown to predict subsequent development of depression six months later (Miller & Cole, 2012). Emerging evidence suggests a direction of causality leading

from stress to heightened inflammation to the development of depression, which may reflect a distinct sub-type of psychopathology, characterised by deficits in reward processing (Cooper, Arulpragasam & Treadway, 2018; Miller & Raison, 2016; Pizzagalli, 2014).

Experimental and longitudinal evidence implicates inflammation in the development of depressive symptoms. This evidence is grounded in observations that a high percentage of patients who receive pro-inflammatory cytokine treatment for infectious diseases or cancer subsequently develop a behavioural phenotype similar to depression (Raison, Capuron & Miller, 2006). Specifically, depressed mood, including anhedonia, and cognitive dysfunction, e.g. loss of concentration, were increased in cancer patients treated with the pro-inflammatory cytokine, interferon-α (INF-α), relative to placebo. Indeed, depending on dosage, up to half of all patients receiving IFN-α therapy meet the diagnostic criteria for MDD (Felger & Treadway, 2017). Similarly, anhedonic symptoms, particularly deficits in motivation, are frequently reported among patient groups undergoing IFN-α treatment for cancer (Capuron, Gumnick, Musselman, Lawson, Reemsnyder, Nemeroff, & Miller, 2002; Capuron et al., 2012). This work is suggestive of a causal role for cytokines in the development of the mood and cognitive symptoms associated with depression (Capuron et al., 2002). Supporting this causal link, a recent longitudinal study observed that greater levels of IL-6 at age 9 were associated with higher risk of developing depression at age 18 in a population sample (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014), even after controlling for typical confounds, e.g. past psychological problems. However, these longitudinal data are not in keeping with previous work (e.g. Wium-Andersen, Orsted, Nielsen & Nordestgaard, 2013) and the experimental increase in depressive symptoms following administration of INF-α was only observed in 30-50% of patients, undermining the ability of inflammation to account for the development of all depressive episodes. A putative explanation for such findings may be the existence of an inflammation-induced depressive subtype, which may be better characterised by a specific symptom phenotype, e.g. anhedonia (Raison & Miller, 2011).

In support of this argument, animal models of depression, in which stressors such as social defeat or foot shock lead to the development of anhedonia and related symptoms,

typically result in increased levels of IL-6 (Yang, Shirayama, Zhang, Ren, & Hashimoto, 2015). Anhedonic symptoms are also observed when cytokines, such as INF-α and IL-6 are chronically administered, which is accompanied by a diminished release of dopamine in the striatum in response to rewards (Felger et al., 2013; Yohn et al., 2016). A decrease in reward circuitry between ventral and dorsal areas of the cortico-striatal pathway, which underlies motivation and goal-directed behaviour, has also been associated with higher levels of C-reactive Protein (CRP) and greater levels of self-reported anhedonia in an un-medicated sample of participants with MDD during resting-state fMRI (Felger, Li, Haroon, Woolwine, Jung, Hu, & Miller, 2016). Specifically, decreased connectivity was observed between the ventral striatum and ventro-medial (vm) PFC. This decreased connectivity was associated with higher levels of anhedonia and increased CRP. Higher levels of CRP were also liked to attenuated connectivity between the dorsal striatum and pre-supplementary motor cortex, which was correlated with reduced motor speed. Finally, the effects of heighted CRP on reduced reward-related connectivity mediated the relationship between higher levels of CRP and greater levels of anhedonia. This suggests a causal mechanism, whereby higher levels of pro-inflammatory cytokines, such as CRP, increase anhedonia by impairing reward-related neural connectivity in the cortico-striatal pathway. Building on this work, Treadway et al. (2017) report an association between stress-induced increases in IL-6 in healthy participants using a laboratory stress induction paradigm, and fMRI-assessed decreased reward prediction error (RPE) signalling in the ventral striatum during a reinforcement learning task. Crucially, no direct relationship was observed between RPE signalling and induced stress, suggesting a role for inflammation in mediating this relationship. Furthermore, stress-induced alterations in IL-6 predicted individual differences in self-reported perceived stress at a four-month follow-up.

Aside from the role inflammation plays in mediating the stress-reward relationship, evidence also suggests that discrete components of reward processing may be differentially affected by both stress and inflammation. Though a relatively new area of research, work by Kumar et al. (2014) suggests that stress has dissociable effects on anticipatory versus consummatory aspects of reward processing and that these effects are linked to individual differences in perceived stress sensitivity (Kumar et al., 2015).

In two studies using an fMRI paradigm, Kumar et al. (2014; 2015) induced stress in participants by incorporating a social evaluation component comprising negative feedback about task performance into a monetary incentive delay task (MID; Knutson, Westdorp, Kaiser & Hommer, 2000). Using the modified MID, Kumar et al. (2014) report acute stress-induced increased activation in the striatum – specifically the right caudate - and amygdala during the anticipation of rewards, accompanied by decreased activity in the striatum – specifically the left caudate and putamen - during the consummatory phase of reward processing. Mirroring the basic neuroscience findings of Cuadura et al. (1999) discussed previously, Kumar et al. (2015) report increased mPFC activity in response to reward feedback in participants with high perceived stress, undergoing a stress-induction paradigm. Similarly, participants with MDD revealed a positive correlation between their perception of the severity of an acute stressor and their reward-related activity in the mPFC. No such finding was evident among a group of healthy controls. Taken together, this work tentatively suggests that stress differentially affects reward processing depending both on the phase of reward processing and characteristics of the individual, e.g. their stress sensitivity. For participants who are depressed or who have greater sensitivity to perceived stress, the mPFC may be recruited more strongly during reward processing during reward consummation (relative to reward anticipation). This is in keeping with previously discussed literature suggesting that dopamine inhibits activity in the mPFC and that stress is linked to motivational impairments in reward processing. It should also be noted that both these studies are underpowered and thus further work is needed to confirm these findings.

Recent work by Boyle and colleagues (2019) offers a conceptual replication and extension of these studies. Using a pre-post design, participants completed two behavioural measures of reward processing prior to and following administration of the influenza vaccination (which leads to a brief increase in inflammation, specifically IL-6; Christian, Porter, Karlsson, Schultz-Cherry & Iams, 2013). Behavioural measures of reward processing comprised the EEfRT (Treadway et al., 2009), which has been outlined in section 1.4 and the Probabilistic Reward Task (PRT; Pizzagalli, Jahn & O'Shea, 2005). While the EEfRT indexes willingness to expend physical effort for reward, a sub-component of anticipatory reward processing, the PRT measures both implicit learning and reward sensitivity; components which, combined, have been

dubbed reward responsiveness (Bogdan & Pizzagalli, 2006) and are broadly linked to consummatory and learning processes. Reflecting inflammation-induced attenuation of motivational processes, greater increases in IL-6 were associated with reductions in reward motivation (quantified by fewer hard task choices on the EEfRT, independent of task specific variables). Increased levels of IL-6 were associated with greater levels of reward responsiveness (measured via response bias on the PRT). While this latter finding was not in line with the hypotheses of Boyle and colleagues, it does compliment findings by Kumar et al. (2015), in which the mPFC was recruited more strongly during reward consummation (relative to reward anticipation). Similarly, administration of IL-1β (a pro-inflammatory cytokine, which induces anhedonic behaviour in rats) in rodents leads to decreased willingness to expend effort to obtain sucrose rewards, but does not impair the consumption of freely-available sucrose, suggesting a selective impairment in motivational processes (Nunes et al., 2014; Vichaya, Hunt & Dantzer, 2014).

Although a relatively new area of research, the mPFC is strongly implicated in these processes, suggesting that EEG asymmetries may be a useful measure of approach and withdrawal motivation associated with stress-induced inflammation. Recent work by Hostinar et al. (2017) sought to establish this link by examining whether resting EEG asymmetry was linked to a composite measure of low-grade inflammation (using a standardised combination of the markers IL-6, CRP and fibrinogen), as well as whether childhood maltreatment, a form of early life stress, would interact with EEG asymmetry to explain inflammation in a large sample of 314 healthy adults. Frontal EEG asymmetry was significantly associated with low-grade inflammation, so that greater right (relative to left) cortical asymmetry was related to higher levels of inflammation, independent of sociodemographic and medical variables. Further analysis indicated that this effect was driven by a sub-group of participants, who reported moderate to high levels of childhood maltreatment. The authors interpret these findings to suggest, in the context of heightened adversity, a tendency toward relatively greater right frontal asymmetry, may represent a vulnerability for low-level inflammation. In this way, individuals with relatively greater right frontal asymmetry may have a heighted vulnerability for inflammation-induced depression, when faced with adversity. This hypothesis is currently highly speculative, however, given the previously discussed

links between inflammation and anhedonic depression, it poses an interesting avenue for future research.

Taken together, this evidence suggests a mechanism whereby stress-induced inflammation may trigger anhedonic symptoms by disrupting dopamine signalling in the cortico-striatal pathways. It is likely that this mechanism of action characterises only a sub-group of people who experience motivational deficits and it is also likely that stress and inflammation differentially affect discrete aspects of reward processing, most likely leading to impairments in anticipatory and effort-related processes. Much of this work implicates irregular activity in the mPFC and recent research by Hostinar et al. (2017) suggest that frontal EEG asymmetry may be a useful method to consider the interaction between stress and inflammation on motivational deficits.

1.11 Aims and research questions

The overall goal of this thesis is to consider the measurement of trait-like aspects of approach and withdrawal motivation for reward using a combination of neural, behavioural and psychometric measures. Individual differences in approach and withdrawal motivation have significant implications for a range of psychopathologies, particularly depression, however, most research takes for granted that measures evolving from different theoretical perspectives and assessing discrete aspects of reward processing are broadly tapping similar constructs. In line with recommendations by Reznik & Allen (2018), this thesis aims to further advance the literature on anhedonia and frontal alpha asymmetry by providing convergent evidence on the measurement of anhedonia, drawing on neural, behavioural and psychometric indices, as well as explicitly linking withdrawal motivation to neural systems hypothesised to underlie motivated behaviour. This thesis aims to examine current assumptions underlying the measurement of approach and withdrawal motivation by pursuing four broad aims.

1. By integrating behavioural, neural and psychometric measures in the same study to assess the convergent validity of these measures.
2. By examining whether frontal EEG asymmetry can be used as a measure of approach and withdrawal motivation.

3. By comparing the utility of discrete self-report measures of anhedonia and approach motivation with the aim of developing and validating a new measure of anhedonia, sensitive to the multifaceted nature of this construct.
4. By considering whether the relationship between discrete components of anhedonia and stress is mediated by a proxy measure of frontal asymmetry.

This programme of research will begin with an attempt to examine the convergent validity of a putative neural measure of approach motivation – EEG-derived left frontal asymmetry; a behavioural task sensitive to willingness to expend effort for reward – the EEfRT (Treadway et al., 2009); and two highly-cited self-report measures of anhedonia (the TEPS; Gard et al., 2006) and of the behavioural approach system (BAS; Carver & White, 1994). A large body of research has attempted to link the BAS with relatively greater left (than right) frontal asymmetry (LFA), resulting in mixed findings (see Wacker, Chavanon & Stemmler, 2010). In contrast, only a small number of studies have considered LFA in relation to behavioural tasks assessing aspects of reward processing (e.g. Hughes et al., 2015; Pizzagalli et al., 2005) and, at the time of study design, none of these studies have considered self-report measures of anhedonia or approach motivation. Chapter 2 seeks to address this gap in the literature and, in doing so, to test the following hypotheses:

1. Greater willingness to expend effort to obtain monetary rewards will be predicted by relatively greater left (than right) frontal EEG asymmetry.
2. Greater willingness to expend effort to obtain monetary rewards will be predicted by the anticipatory (but not the consummatory) subscale of the Temporal Experience of Pleasure Scale (TEPS).
3. Greater willingness to expend effort to obtain monetary rewards will be predicted by the Reward Responsiveness subscale of the BAS.
4. All three of these associations will be strongest for trials on which the probability of reward receipt is low (i.e. 12% relative to 88% likelihood of reward receipt).

Building on the work in chapter 2, chapter 3 seeks to examine withdrawal motivation, again using the LFA, in addition to a behavioural measure ostensibly assessing an avoidance behaviour – loss aversion – and Carver and White's (1994) BIS / BAS scales.

While a great deal of work focuses on the relationship between the BAS or approach motivation and LFA, much less work has considered behavioural avoidance or withdrawal motivation in the context of frontal asymmetry. Such work as exists in this area has typically focused exclusively on the relationship between LFA and the BIS / BAS scales – a measure which is outdated, as it is not in-line with the revised Reinforcement Sensitivity Theory (rRST; Gray & McNaughton, 2000) -or has considered EEG asymmetry in bands other than alpha (8-13Hz) and thus do not represent a true test of Davidson's (1992) theory on approach / withdrawal motivation. Given the mixed findings in this area and the reliance on an out-dated psychometric measure of withdrawal / avoidance behaviour, chapter 3 attempts to investigate the relationship between EEG alpha asymmetry and a behavioural measure of withdrawal / avoidance behaviour: loss aversion. Chapter 3 tests the following hypotheses:

1. Relatively greater right (than left) frontal EEG asymmetry will be associated with greater behavioural loss aversion.
2. This effect will be most pronounced for frontal regions (compared to medial or posterior regions).

Based on the absence of relationships between self-report measures of behavioural approach / withdrawal with EEG and behavioural measures of related concepts observed in chapters 2 and 3, chapter 4 seeks to develop and validate a new self-report measure, which is sensitive to a more nuanced interpretation of motivation for reward based on contemporary understanding of anhedonia (e.g. Treadway & Zald, 2011, 2013; Rømer Thomsen et al., 2015). Chapter 4 draws on existent measures of anhedonia and approach motivation to create a pool of items sensitive to a broad constellation of reward processing attributes. Chapter 4 includes two studies seeking to establish and validate the Goldsmiths Anhedonia Measure (GAME). Study 1 seeks to test the factor structure of the GAME using an exploratory factor analysis. Study 2 attempts to confirm the four-factor structure suggested by study 1, as well as to establish the convergent validity of this new measure with existent measures of anhedonia, approach motivation and the big five model of personality.

Building on the work in chapter 4, chapter 5 seeks to provide validation for the refined version of the GAME, using a common psychometric measure of depression: The Beck

Depression Inventory II (Beck, Steer & Brown, 1996), and to test the diathesis-stress model of anhedonia proposed by Pizzagalli (2014), as well as investigating a proxy version of frontal EEG asymmetry – left-bias on a line bisection task – as a potential mediator of the relationship between stress and anhedonia. This chapter examines the following hypotheses:

1. Higher levels of perceived stress will predict heighted anhedonia on the interpersonal, emotional and drive subscales of the GAME (Hypotheses 1 – 3).
2. Stress will not predict anhedonia on the sensory pleasure subscale of the GAME (H4)
3. The relationship between stress and anhedonia will be partially mediated by left-sided bias on the line bisection task; a proxy of right frontal asymmetry (H5 – 7).
4. Higher levels of perceived stress will predict anticipatory pleasure, but not consummatory pleasure, as measured by the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) (H8 - 9).
5. The relationship between stress and anticipatory pleasure (TEPS ANT) will be partially mediated by left-sided bias on the line bisection task; a proxy of right frontal asymmetry (H10).
6. Higher scores on three GAME subscales (interpersonal, emotional and novelty-seeking domains), indicative greater anhedonia, will be associated with higher depression scores (H11 – 13).
7. Depression scores will be unrelated to anhedonia scores on the Sensory Pleasure subscale of the GAME (H14).

Chapter 2

Triangulating approach: Do cortical left frontal asymmetry and trait behavioural approach predict willingness to expend effort for rewards?

Overview

A resurgence of interest in the definition of anhedonia and its role in mental health disorders such as depression and schizophrenia calls for a reconceptualization of how the symptom is defined. Recent research emphasizes the importance of motivational, rather than hedonic, deficits in depression and schizophrenia. A plethora of measures, spanning neurobiological, self-report and behavioural domains, exist to quantify anhedonia, but little work considers the comparative validity of these measures. The present study seeks to address this by considering the relationship between commonly-used measures of motivational anhedonia / approach behaviour from the behavioural (the Effort Expenditure for Rewards Task; EEfRT), neurobiological (relative left frontal asymmetry; LFA) and self-report (the Snaith-Hamilton Pleasure Scale, the Behavioural Approach System, and the Temporal Experience of Pleasure Scale) domains. Behavioural, EEG and self-report data were obtained from 52 healthy adults. Data were analysed using a series of Generalised Estimating Equations to investigate the predictive power of LFA and the self-report measures in predicting hard task choices on the EEfRT. In contrast to previous research, the self-report measures did not predict EEfRT performance. While no main effect of LFA was observed, an interaction between LFA and hard task choice was observed for those trials on which the probability of receiving a reward was low (i.e. 12%). This suggests a role for the putatively dopamine-mediated LFA in predicting willingness to expend effort for reward in the face of risky or uncertain reward receipt. These findings are discussed in relation to the validity of self-report measures of approach motivation and the need for greater scrutiny of the convergent validity of analogous measures of approach motivation.

2.1 Introduction

2.1.1 Reward processing deficits in depression

Despite its status as a leading cause of disability, affecting more than 300 million people globally (WHO, 2018), treatments for depression are lacking, with efficacy of 50 – 60 per cent (Trivedi et al., 2006; Rush et al., 2006). Impairments in reward processing are now widely acknowledged as a transdiagnostic symptom implicated in several psychiatric disorders, including depression and schizophrenia. Despite a resurgence of research interest in reward processing impairments in depression, however, the most common treatments, e.g. selective serotonin reuptake inhibitors (SSRIs) such as citalopram and fluoxetine, common first-line anti-depressant treatments, do not sufficiently address such deficits (Cooper, Tucker & Papakostas, 2014; Culbreth, Moran & Barch, 2017; Fava et al., 2014; Yohn, Collins, Contreras-Mora, Errante, Rowland, Correa & Salamone, 2016; Yohn, Lopez-Cruz, Hutson & Salamone, 2016). Of these reward processing deficits, anhedonia - the loss of interest or pleasure in previously rewarding stimuli - is a consistent predictor of poor response to treatment (McMakin et al., 2012; Uher et al., 2011; 2012).

A key difficulty in treating reward processing deficits lies in the imprecise terminology and the complexity of the reward constructs implicated in depression. Anhedonia is one of two criteria necessary to meet the diagnosis of depression according to the DSM-5 (American Psychiatric Association, 2013). Despite its importance, however, the criterion itself is ambiguously defined as diminished interest or pleasure in previously rewarding activities. This definition conflates motivation to pursue a reward with the enjoyment of the reward once obtained. This conflation receives little support from the basic neuroscience literature, which suggests that motivation and pleasure, or "wanting" and "liking" of a reward, are anatomically separable processes (e.g. Berridge & Kringelbach, 2008) and comprise just two aspects of a constellation of reward processing deficits which may present as variations on the symptom currently defined as "anhedonia". Several theorists have outlined a wider cycle of reward-processing, including the ability to anticipate or predict rewards; determine the relative value of different rewards; weigh the cost / benefit of effort to obtain rewards; the performance of goal-directed behaviours to receive a reward; the enjoyment / consummation of the

reward once received and the learning from experience, to enable future rewards (Der-Avakian, Barnes, Markou & Pizzagalli, 2016; Pizzagalli, 2014; Rømer Thomsen, Whybrow & Kringelbach, 2015).

2.1.2 The role of dopamine in effort-cost decision-making

This dissociation of reward processing receives support from the basic animal literature, which illustrates at least partially dissociable neurobiology between different aspects of the reward cycle (see Der-Avakian & Markou, 2012; Der-Avakian et al., 2016; Treadway & Zald, 2011). Much of this literature focuses on the neurotransmitter dopamine (though it should be acknowledged that several systems other than dopamine are critically involved in the reward process, e.g. opioids, gamma-aminobutyric acid (GABA) and serotonin). In part, this focus has emerged due to evidence that processes pertaining to reward "wanting" (thought mainly to be served by dopaminergic pathways) may be selectively impaired in psychopathologies such as depression, whilst reward "liking" (thought to be facilitated via GABA and opioid systems) remains relatively preserved (e.g., Sherdell Waugh & Gotlib, 2012; for reviews see Nusslock & Alloy, 2017; Treadway & Zald, 2011).

Much of the literature focusing on dopaminergic mechanisms in reward processing points to the importance of the mesolimbic dopaminergic pathway in effort-cost decision-making (ECDM). Animal models suggest that dopamine-mediated ECDM may be a key contributor to motivational impairments in depression and schizophrenia. In such models, rats are typically presented with alternative food choices: a highly desirable food that requires some additional physical effort to obtain (High Effort / High Reward; HE/HR) and a less palatable alternative that is either freely available or is easily accessed (Low Effort / Low Reward; LE/LR). In their healthy state, rats will choose the HE/HR option 90% of the time, however, attenuation of dopamine in nucleus accumbens (NAcc) leads to increased preference for the LE/LR option, independent of changes in appetite, food preference or locomotor ability (Correa, Carlson, Wisniecki & Salamone, 2002; Cousins, Sokolowski & Salamone, 1993; Salamone, Correa, Farrar & Mingote, 2007; Salamone, Koychev, Correa & McGuire, 2015). In contrast, enhancement of dopamine with D-amphetamine (specifically when acting on D_1 and D_2 receptors), increases rats' willingness to expend physical effort to

obtain palatable rewards (Bardgett, Depenbrock, Downs, Points & Green, 2009). The effects of dopaminergic manipulation also seem to be specific to ECDM, as rats with depletion of up to 99 per cent of the dopamine neurons in the NAcc and the neostriatum show normal intact hedonic responses to sucrose-infused water (compared to quinine), suggesting a preserved "liking" response (Berridge & Robinson, 1998). Taken together, this evidence suggests that merely stating that dopamine depletion impairs motivation for reward generally is an over simplification, rather there is a selective role for dopamine in the willingness to expend effort in pursuit of rewards.

2.1.3 Effort-Cost Decision-Making (ECDM) in humans

Using a human analogue of these ECDM paradigms, the Effort Expenditure for Reward Task (EEfRT; Treadway, Buckholtz, Schwartzman, Lambert & Zald, 2009), similar effects of dopamine manipulation on ECDM have been observed in humans. The EEfRT is a multi-trial game, which offers participants a choice of expending a small amount of physical effort (10 button presses with the index finger of the dominant hand) for a small fixed monetary reward (£1) or a relatively greater amount of physical effort (100 button presses with the pinkie finger of the non-dominant hand) for a larger financial reward, which varies in size from £1.24 and £4.12. Completion of the trial does not guarantee a reward; reward receipt is contingent on a probability cue of 12%, 50% or 88%, which is displayed to participants before they make their choice. Thus, similar to animal models of effort-choice behaviour, participants are faced with varying combinations of effort requirement and potential rewards and the task seeks to establish individual differences in choice behaviour.

Using the EEfRT, individual differences in willingness to expend effort for reward linked to trait anhedonia have been observed (Treadway et al., 2009; Geaney, Treadway & Smillie, 2015), as well as group differences between participants diagnosed with MDD or schizophrenia and healthy controls (Barch, Treadway & Schoen, 2014; Treadway, Bossaller, Shelton & Zald, 2012; Yang, Huang, Zhu, Wang, Cheung, Chan & Xie, 2014). Specifically, individuals with higher levels of trait anhedonia (assessed using the Chapman Anhedonia Scales; Chapman, Chapman & Raulin, 1976) were less willing to expend effort for reward under conditions of maximum uncertainty (i.e. when the chance of reward receipt was 50%). Geaney, Treadway & Smillie (2015) observed

that such individual differences were specifically linked to anticipatory hedonic tone (as measured by the Temporal Experience of Pleasure Scale; Gard, Gard, Kring & John, 2006) and approach motivation more generally (assessed via the BAS subscale of the BIS / BAS Scales; Carver & White, 1994). Interestingly, they observed these effects only under the most unlikely condition of reward receipt (i.e. 12%), rather than the 50% condition, as observed by Treadway et al. (2009).

This sensitivity to the probability of reward receipt is also reflected in dopaminergic-mediated accumbens processing of uncertain rewards. Dopamine neurons innervating the nucleus accumbens appear to fire in a pattern that reflects the probability of reward receipt (Fiorillo Tobler & Schultz, 2003; Niv, Duff & Dayan, 2005; Tobler, Fiorillo & Schultz, 2005), so that the greatest level of dopaminergic function is observed not when high rewards are on offer, but when reward receipt is most unlikely or uncertain. Antagonism of dopamine receptors leads to a preference of small, guaranteed rewards, over large, uncertain rewards, whereas, administration of amphetamine – which increases extracellular dopamine – increases willingness to choose larger, riskier rewards (St. Onge & Floresco, 2009; St Onge, Chiu & Floresco, 2010). Similarly, the human nucleus accumbens demonstrates increased blood flow (BOLD response) during the anticipatory phase of a high risk / high reward task (Ernst et al., 2005).

Between group differences on the EEfRT point to an impairment in ECDM in individuals with depression and schizophrenia. These studies typically report lower willingness to expend effort for (relatively greater) rewards among sub-syndromally depressed (study 1, Yang et al., 2014), medication-naïve depressed patients (study 2, Yang et al., 2014), patients with schizophrenia (Barch et al., 2014) and in patients with depression currently experiencing a major depressive episode (Treadway et al., 2012). Overall, patients with schizophrenia are less likely to choose to expend effort for reward, under all conditions of reward magnitude and probability of reward receipt and this finding is particularly salient for those patients with greater avolition (a negative symptom of schizophrenia similar to anticipatory anhedonia, indicating a decrease in motivation) (Barch et al., 2014). Similarly, Treadway et al. (2012) observed that patients with MDD were less likely to choose the hard task on the EEfRT. They report that patients seemed less able to integrate information about reward magnitude and likelihood of reward receipt compared to controls, such that these parameters were less

strongly predictive of choosing the hard task for patients than for controls. In particular, reduced anticipatory pleasure was associated with fewer HE/HR choices, however, this observation is based on a post-hoc item-level analysis of the relationship between EEfRT performance and individual items on the Beck Depression Inventory (BDI-II; Beck, Steer, Ball & Ranieri, 1996) and should be interpreted with caution. Yang et al. (2014) note a similar reduction in willingness to expend effort for reward in patients with MDD. Similar to Geaney et al. (2015) and Treadway et al. (2009), they link this deficit to self-reported anhedonia, assessed by the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006). The observed relationships between self-reported anhedonia and hard task choice on the EEfRT differed, depending on whether participants were sub-syndromal, experiencing their first episode of MDD, had remittent depression or were healthy controls. For sub-syndromal participants, reductions in anticipatory pleasure were associated with fewer hard task choices under an 80% probability of reward receipt, whereas participants experiencing their first depressive episode showed an association between reduced willingness to expend effort for reward and reductions in both anticipatory and consummatory pleasure under the 50% likelihood of reward delivery. No such associations were observed for healthy controls and patients with remittent depression showed an association between EEfRT performance and consummatory pleasure, as assessed by the Snaith Hamilton Pleasure Scale (SHAPS; Snaith, Hamilton, Morley, Humayan, Hargreaves & Trigwell, 1995), albeit only under conditions were reward receipt was most unlikely (in this study, 20%). These between-group findings point to some form of impairment in ECDM in both schizophrenia and depression, however this relationship, particularly its links to anhedonia and relationship to reward probability, are somewhat unclear.

2.1.4 Dopaminergic mechanisms in ECDM in humans

Attempts to establish the brain mechanisms underlying ECDM and motivation for rewards have naturally sought to investigate the role of dopaminergic neurotransmission and reward-related neural circuitry in the midbrain. Decreased synthesis of dopamine (via acute phenylalanine / tyrosine dietary depletion) in a sample of low-frequency smokers decreased willingness to sustain effort for nicotine rewards on a progressive ratio task, independent of any reductions in craving or pleasure (Venugopalan, Casey, O'Hara, O'Loughlin, Benkelfat, Fellows & Leyton, 2011). In

contrast, administration of *d*-amphetamine, an indirect dopamine antagonist, which increases levels of extracellular dopamine, increased healthy participants' willingness to choose the hard task on the EEfRT, particularly under the lowest probability condition (i.e. when likelihood of reward receipt was 12%) (Wardle, Treadway, Mayo, Zald & de Wit, 2011). Reflecting observations from the animal literature, no effect of *d* amphetamine on sensitivity to reward magnitude was observed.

Neuroimaging work has been incorporated into ECDM paradigms to elucidate the neural mechanisms underlying willingness to expend effort for reward. Such studies point to a selective role for the left hemisphere in mediating ECDM. Using a positron emission tomography (PET) study, Treadway et al. (2012b) examined individual differences in dopaminergic function (via administration of a placebo-controlled, *d* amphetamine challenge). Individual variation in D_2 and D_3 receptor availability in the bilateral ventromedial prefrontal cortex (vmPFC), left ventrolateral prefrontal cortex (vlPFC), the left caudate and the left inferior temporal gyrus, was associated with choice of the hard task on the EEfRT. Specifically, greater receptor availability in these areas was associated with an increased likelihood of choosing the hard task, particularly under conditions of low probability of reward receipt (12%).

2.1.5 Lateralisation of anticipatory reward processing in humans

2.1.5.1 Frontal alpha asymmetry and approach motivation

A similar left-lateralisation of anticipatory aspects of reward processing can be observed in the electroencephalography (EEG) literature on approach motivation. Within this literature, a pervasive theory posits that motivational processes are lateralized over frontal areas, so that increased motivation to pursue a reward is reflected in higher left (relative to right) frontal activity derived from a spectral analysis of resting state EEG data (Davidson, 1998). Considerable research spanning the past 40 years has linked frontal EEG asymmetry with reward processing (Reznik & Allen, 2018; Davidson et al., 1979) and the technique is now a commonly used correlate of approach and withdrawal motivation (for reviews see Harmon-Jones & Gable, 2017; Kelley, Hortensius, Schutter & Harmon-Jones, 2017; Nusslock, Walden & Harmon-Jones, 2015; Reznik & Allen, 2018), although debate over the validity of this link exists

(see Wacker, Chavanon & Stemmler, 2010), particularly over its proposed utility as a biomarker for depression (see a recent meta-analysis by van der Vinne, Vollebregt, van Putten & Arns, 2017). The frontal asymmetry index is typically calculated as a difference score between homologous left and right electrode sites in the alpha band (8 – 13 Hz) of the EEG. Alpha power is inversely related to cortical activity, so that lower frontal asymmetry scores (right minus left alpha) are reflective of relatively less left than right cortical activity. Typically, studies assess alpha activity either at rest - as a putative trait index of approach motivation (e.g. Allen & Cohen, 2010; Hughes et al., 2015) - or during tasks that evoke an emotional or motivational response, thus acting as a state measure (e.g. Harmon-Jones & Sigelman, 2001; Stewart, Coan, Towers & Allen, 2011).

Both these resting-state and state-manipulation paradigms are grounded in the original reinforcement sensitivity theory (RST) proposed by Gray (1972). The RST proposes three systems underlying behaviour: the behavioural activation system (BAS); the behavioural inhibition system (BIS) and the fight / flight system (FFS). Each system mediates a different set of responses to environmental cues, so that BIS facilitates withdrawal from punishment, FFS determines responses to unconditioned threats to enable the organism to fight or flee, and BAS underlies approach motivation for reward. The Davidson (1998) approach system is conceptually similar to the BAS proposed by Gray (1972), in that both systems are engaged by perceived goals in the environment and initiate behaviours aimed at achieving these goals. Thus, both systems reflect similar anticipatory, "wanting" and ECDM processes, to those implicated in anhedonia.

Neuroanatomically, Davidson's approach system reflects engagement of the left PFC (similar to that demonstrated by Treadway et al., 2012b), as well as the mesolimbic dopamine reward pathways, thought to underlie the BAS. Thus, work in this area argues that the lateralization of approach / withdrawal motivation in EEG asymmetry reflects Gray's BAS / BIS system, so that relatively greater left (than right; LFA) asymmetry reflected the BAS, whilst greater right (relative to left; RFA) asymmetry reflected the BIS. There is a large body of literature seeking to validate this theory, though the findings have been mixed. Using Carver & White's (1994) BIS / BAS self-report measure, work by Sutton and Davidson (1997) and Harmon-Jones & Allen (1997) reported relatively greater LFA (indicating greater engagement of the approach system)

among healthy participants who scored higher on the BAS subscale. Amodio, Master, Yee & Taylor (2008) replicated this finding, however, four separate studies by Wacker and colleagues failed to observe this relationship and their meta-analysis of studies assessing this relationship indicated no reliable association between LFA and self-report measures of approach motivation, including the BAS (Wacker, Chavanon & Stemmler, 2010).

In partial support of this hypothesis, LFA has been directly linked to the midbrain dopaminergic reward pathway. Wacker, Müller, Pizzagalli, Hennig & Stemmler (2013) recorded resting state EEG data from 181 heterosexual males, following double-blind administration of either a placebo or a dopamine D_2 blocker. Greater LFA was associated with trait BAS (assessed via Carver and White's (1994) BIS / BAS scales) in the placebo group, while this association was reversed for the dopamine-blockaded group. In contrast to the literature discussed above, however, this relationship was only significant for participants engaged in an approach-motivated state, i.e. when they were interacting with an attractive experimenter of the opposite sex. In the same study, Wacker and colleagues observed an association between LFA and variation in the COMT Val158Met gene. The COMT Val158Met polymorphism is responsible for regulating catabolism of dopamine in the PFC and thus provides a direct link between LFA and dopaminergic processes. In this study, the relationship between LFA and the Val allele was positive for those participants interacting with an attractive experimenter (i.e. who were in an approach motivated state). Taken together with the work by Treadway et al. (2012b), this suggests a direct link between left lateralisation and approach motivation, which may be linked to the modulation of ECDM by dopaminergic processes.

Further evidence to support this claim comes from work by Hughes, Yates, Morton & Smillie (2015). They measured LFA in 51 right-handed participants, before asking them to complete the EEfRT. Those participants with greater LFA at resting state (indicative of a trait-like measurement, rather than the state-mediated measurement used by Wacker et al., 2013), showed greater willingness to choose the hard task on the EEfRT. Crucially, this association was strongest for those trials in which the probability of reward receipt was low (12%).

2.1.6 The Present Study

Taken together, the research reviewed here suggests that three approaches to assessing approach motivation have evolved in parallel, i.e. behavioural work focusing on ECDM, self-report measures assessing variations on the BAS, approach motivation and anhedonia, and neural indices of motivation, such as the EEG-derived LFA. Attempts to integrate these approaches and to consider the extent to which they represent equivalent measures of the same construct are lacking. While a plethora of research has sought to link LFA with psychometric measures of approach motivation, most commonly the BIS / BAS scales, little research has directly assessed its relationship with behavioural measures of approach motivation, such as the EEfRT. A notable exception is a study by Hughes, Yates, Morton & Smillie (2015), which reported an association between LFA and greater willingness to choose the HE / HR option on the EEfRT, particularly when reward receipt was unlikely (12%). In a parallel study, Geaney, Treadway & Smillie (2015) examined the validity of self-report measures of approach motivation (the TEPS and BAS) in relation to the EEfRT. Their findings suggested a predictive role for both the anticipatory subscale of the TEPS (TEPS-ANT) and the BAS in predicting hard task choices on the EEfRT, particularly when the probability of reward receipt was low (12%). Finally, given speculation by Treadway and Zald (2011) as to whether the TEPS-ANT and approach motivation reflect the same construct and considering work by Heym, Ferguson & Lawrence (2008), which suggests suppressor effects of the three BAS subscales when they are combined, work is needed to identify whether a subtype of the BAS, reflecting anhedonic deficits, is linked to LFA.

The current study seeks to build on existing research by replicating the main findings from Hughes et al. (2015) and Geaney et al. (2015) and by triangulating all three approaches – self-report, behavioural and neural – concurrently in a single sample. We thus hypothesized that hard task choices on the EEfRT would be predicted by:

1) relatively greater left (than right) frontal asymmetry in the alpha band of the EEG;
2) the TEPS-ANT, but not the TEPS-CON;
3) the Reward Responsiveness subscale of the BAS.

4) We additionally expect that these associations will be strongest for trials on which the probability of reward receipt is low (i.e. 12% likelihood of reward receipt).

2.2 Method

2.2.1 Participants

Fifty-two healthy participants (36 female; age range 18-42 years; *M* = 22.76 years, *SD* = 4.48 years; 44 right-handed; 18 with a familial history of depression) were recruited opportunistically via noticeboards around Goldsmiths campus and through online forums. One participant was subsequently excluded, due to a current depressive illness, leaving a final *N* = 51. Participants were initially told they would receive between £12 and £20 for their participation in the study, based on their winnings on the EEfRT task. This was done to incentivize task performance. Upon completion of the experiment, however, all participants received £20 in compensation for their time. The study received ethical approval from the Ethics Committee at Goldsmiths, University of London. In addition, all participants gave separate written consent for the behavioural, psychometric and EEG portions of the study.

2.2.2 Materials

Each participant completed several psychometric measures (see below). They subsequently completed the EEfRT and participated in the EEG recording session.

2.2.2.1 Effort Expenditure for Reward Task (EEfRT)

The EEfRT is a computer-based decision-making task that assesses how participants' willingness to expend physical effort to obtain monetary rewards is influenced by both the magnitude of the reward and the likelihood of receiving the reward (see Treadway et al., 2009). For each trial, participants decided between an "easy task" (for a chance to win £1) and a "hard task" (for a chance to win an amount that varies between £1.24 and £4.12). To successfully complete the easy task, participants were required to use the index finger of their dominant hand to make 30 successive keystrokes within 7

seconds (pressing the L or S key on a QWERTY keyboard for right vs. left handed participants, respectively). For the hard task, participants were required to use the fourth ('little') finger of their non-dominant hand to make 100 successive keystrokes within 21 seconds (pressing the L or S key on a QWERTY keyboard for right vs. left handed participants, respectively); a more physically demanding requirement.

Critically, successful completion of a task does not guarantee that the participant will win the money for that trial. Rather, winning the reward is subject to a low (12%), medium (50%) or high (88%) probability of reward delivery, which varies randomly across trials. Participants were presented with an accurate probability cue on-screen prior to the commencement of each task. They were then given 5 seconds in which to decide whether to perform the easy or hard version of the task. The win-lose probability equally applied to all trails, irrespective of whether participants opted for the easy or the hard task, i.e. for a medium probability trial, participants might choose between a 50% chance of winning £1 by making 30 keystrokes with the index finger of their dominant hand, versus a 50% of winning £3.23 by making 100 keystrokes with the little finger of their non-dominant hand. Figure 2.1 depicts a schematic display of a single EEfRT trial.

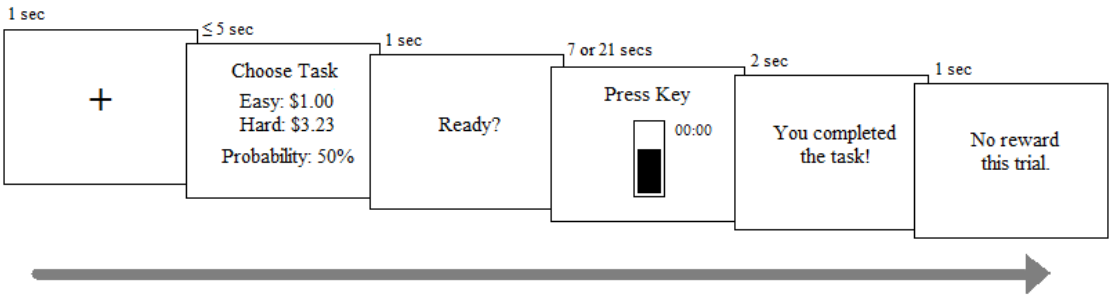

Figure 2.1: Schematic representation of a single EEfRT trial from Treadway, Buckholtz, Schwartzman, Lambert, & Zald (2009).

Prior to task commencement, instructions were verbally outlined to participants and were also displayed on-screen. They were told that the task would last 20 minutes and that they would win the combined total of two randomly selected trials at the end of the experiment.

2.2.2.2 Psychometric Measures

To assess trait hedonic tone and current depressive symptoms, several psychometric measures were administered electronically using Qualtrics software.

2.2.2.2.1 BIS / BAS Scales

The BIS / BAS scales (Carver & White, 1994) correspond to the two bio-behavioural systems described by Gray (1970). The scales total twenty-four items, rated on a Likert scale from 1 ("*very true for me"*) to 4 ("*very false for* me"). The BAS scale includes thirteen items on behavioural approach of rewards, e.g., "*I go out of my way to get things I want"*, and emotions associated with reward pursuit, e.g., "*When I see an opportunity for something I like, I get excited right away*". The BAS encompasses three subscales: Reward Responsiveness (RR), Drive (D), and Fun Seeking (FS). Items for each subscale are summed, with higher scores indicative of higher approach / inhibition respectively. The subscales each assess a different aspect of approach behaviour, e.g. BAS RR assesses motivation toward a future reward through items such as *"When I see an opportunity for something I like, I get excited right away"*. BAS FS assess motivation to approach immediately rewarding stimuli, using items such as *"I am always willing to try something new if I think it might be fun"*. Finally, BAS D measures goal-related approach behaviour, e.g. *"When I want something, I usually go all out to get it"*. Of interest in the present study is the BAS RR, given it's overlap with anticipatory aspects of pleasure and reward processing. Relevant Cronbach's αs were acceptable for the present sample: BAS total, $\alpha = .799$; BAS RR $\alpha = .68$.

2.2.2.2.2 Temporal Experience of Pleasure Scale (TEPS)

The Temporal Experience of Pleasure Scale (Gard, Germans Gard, Kring & John, 2006) is an 18-item scale designed to measure individual differences in the experience of pleasure. The questionnaire comprises two sub-scales; one of which assesses anticipatory pleasure, e.g. *"When something exciting is coming up in my life, I really look forward to it"*, while the other assesses consummatory pleasure, e.g. *"The sound of crackling wood in the fireplace is very relaxing"*. Each sub-scale is scored on a Likert

scale from 1 (*"Very false for me"*) to 6 (*"Very true for me"*). One item, *"I don't look forward to things like eating out at restaurants"* is reverse coded. Items for each subscale are summed and the sub-scales can be combined to give a total score indicative of trait hedonic tone. For the current sample, Cronbach's alpha suggested high reliability (α = .73) for the anticipatory subscale and (α = .708) for the consummatory subscale. Possible scores range from 18 – 103.

2.2.2.2.3 Snaith-Hamilton Pleasure Scale (SHAPS)

The SHAPS (Snaith, Hamilton, Morley, Humayan, Hargreaves, & Trigwell, 1995) is a commonly used, standardised questionnaire assessing hedonic tone. The measure comprises fourteen items pertaining to the enjoyment of pleasurable things, e.g. *"I would enjoy seeing other people's smiling faces" and "I would enjoy a warm bath or refreshing shower"*. Items pertain to both interpersonal / social activities and to physical activities across all sensory modalities and load onto a single factor, assessing consummatory pleasure. Items are answered on a Likert scale, ranging from 1 ("*Strongly Disagree"*) to 4 ("*Strongly Agree*"). Cronbach's alpha suggested high reliability for the scale in the present sample (α = .85). Possible scores range from 14 – 56.

2.2.2.2.4 Beck Depression Inventory (BDI-II)

The BDI-II (Beck, Brown & Steer, 1996) is a 21-item self-report questionnaire used to assess depression severity in both clinical and healthy samples. Questions are answered by selecting one of four options to indicate symptom severity, ranging from not present (0) to severe (3). The BDI-II was designed to reflect DSM-IV (APA, 1994) diagnosis of depression and, as such, assesses symptoms over a two-week period. Symptoms include: sadness, pessimism, perceived failure / rumination, loss of interest and pleasure / anhedonia, feelings of guilt and punishment, dislike of self and self-criticism, suicidal ideation, agitation, irritation and indecisiveness, crying, irritability, ability to concentrate, changes in levels of energy, appetite, interest in sex, and sleeping pattern, as well as feelings of fatigue and worthlessness. The current sample had excellent reliability; Cronbach's α = .903, in line with that reported by Beck, Brown and Steer (1996). The maximum possible score for the BDI-II is 63 and the authors provide the

following suggested cut-off scores: 0-13: minimal depression; 14-19: mild depression; 20-28: moderate depression; 29-63: severe depression.

2.2.3 Procedure

2.2.3.1 Psychometric data collection and completion of the EEfRT task

Participants were seated in front of a PC in individual cubicles in a computer lab. The researcher outlined the nature of the study in three parts: the psychometric measures, the EEfRT task, and the EEG data collection. Participants were told that the study would take between 2-3 hours of their time and that they would be financially reimbursed (see section 2.2.1 for details) at the end of the experiment. At this point participants were given the option to withdraw from the study.

Participants first completed the psychometric portion of the study. Psychometric measures were presented online using Qualtrics software (www.qualtrics.com). An electronic consent form outlining the nature of the study was also administered through Qualtrics and participants were required to read and complete this to indicate their willingness to participate in the research. Participants were initially asked to complete eight psychometric measures, tapping aspects of anhedonia, depression, extraversion and reward processing. Some of these measures were used in MSc research projects and are not of relevance to the present study. Participants were given approximately 40 minutes to complete these questionnaire measures via Qualtrics.

Upon completion of the psychometric measures, participants were given a short break before beginning the EEfRT task. The EEfRT task (see description in section 2.2.2.1) was presented using E-Prime 2.0 software (Psychology Software Tools, 2012). The researcher outlined the nature of the task verbally and participants were presented with a set of instructions online. The researcher then checked that participants had understood the instructions and set the task to reflect whether the participant reported being right (44 participants) or left-handed. All participants completed four practice trials to ensure they understood the task before commencing the actual trials. Participants were given 20 minutes to complete as many trials as possible. As the number of completed trials varied for each participant (depending on their combination

of hard or easy task choices), trials were capped at 44 for consistency during analysis (this is in line with previous studies using the EEfRT, e.g. Treadway et al., 2009). All participants completed a minimum of 44 trials. This number is approximately equivalent to that observed in other studies using the EEfRT, e.g. Geaney et al., 2015 (43 trials); Hughes et al., 2015 (46 trials); Treadway et al., 2009 (50 trials). Upon completion of the task, participants were presented with a screen instructing them to wait for the researcher. Participants were then told how much money they had won on the task and that this amount would be added to their compensation after participation in the EEG study.

Participants were then escorted on foot to a separate building to complete the EEG portion of the experiment. This enabled them to take a break outside to help combat fatigue effects. Upon arrival in the EEG lab, participants were given a second consent form to indicate their willingness to undergo the EEG recording. Continuous EEG was recorded from 64 electrode channels while the participant sat in shielded booth in low-lit conditions. The participants alternated between sitting with their eyes open for 60 seconds and closed for 60 seconds for a total of eight minutes. Participants were given an audio prompt indicating when they should open / close their eyes. Following the eight-minute recording, participants engaged in an EEG-behavioural task not related to the present study. After completion of this task, participants were debriefed and paid for their time.

2.2.3.2 EEG recording and pre-processing

Continuous EEG data were obtained from 64 active Ag/AgCl electrode channels placed in accordance with the 10-20 system (Jasper, 1958) embedded in an Easycap® (Easy Cap, Munich, Germany). To allow for the removal of eye-movement induced artifacts at analysis, two electrodes were placed on the sub- and supra-orbit of the right eye to monitor vertical eye movements - electrooculogram (EOG) - and an additional two electrodes recorded the horizontal EOG from the external canthi of each eye. Two additional reference electrodes were placed one on the lobe of each ear. The experiment was run on a Dell PC. All data were sampled at 512Hz and were amplified using a BioSemi ActiveTwo® amplifier with a 0.01Hz to 100Hz bandpass filter. EEG recording was continuously monitored by the experimenter throughout the experiment.

EEG was recorded for eight minutes in total, comprising alternating conditions in which participants were required to keep their eyes open or closed for 60-second periods.

EEG data were pre-processed using Brain Vision Analyser software (Brain Products, GmbH). An average reference (Cz) was applied in addition to a 0.5-50Hz bandpass filter and a 50Hz notch filter. Cz was chosen as an initial reference as it does not fall within either hemisphere and it falls outside of the regions of interest for calculating LFA. The data were subsequently segmented according to the two conditions (i.e. eyes open and eyes closed). Artifacts, e.g. eye-movements, were automatically detected according to a maximum/minimum criterion ($\pm$70mV on target frontal channels and EOG channels) and corrected or rejected as necessary. Excessively noisy or flat-lined channels were removed and excluded from the analysis. The Gratton and Coles (1983) method of ocular correction was applied to the data; this method estimates eye artifacts and removes them in a manner dependent on the distribution of activity across the scalp. A final visual inspection of the data was carried out to detect any artifacts that were undetected in previous steps.

Data were further segmented into two-second epochs, that overlapped by 50% to minimise data loss through 'windowing' (i.e. data attenuation) at segment boundaries. Using a Fast Fourier Transform (FFT) with a 100% Hann (also called Hanning) window, the EEG data were converted into power spectral densities (mV^2/Hz). The segments for each EEG channel were averaged to produce a single power spectrum estimate per channel. Spectral power pertaining to the alpha frequency band (i.e. 8-12.75Hz) was extracted for each electrode and transferred to an SPSS data file.

2.2.3.3 Data analyses

2.2.3.3.1 EEfRT

In keeping with previous studies using the EEfRT, e.g. Treadway et al., 2009; Hughes et al., 2015, we analysed these data using a series of Generalised Estimating Equations (GEEs; Zeger & Liang, 1986). GEEs are a form of regression, which permit trial-by-trial modelling of parameters that vary over time and may be correlated. GEE models were run using SPSS v.24 for Mac. Eight models were run using an independent

working correlation matrix. It should be noted that this choice of matrix differs from those used in previous research (e.g. Treadway et al., 2009; Hughes et al., 2015). We chose this matrix as, in the absence of knowledge about the autocorrelations in the data, the independence matrix is typically a good choice (see Højsgaard, 2006). The analysis was re-run using both the unstructured (as in Treadway et al., 2009) and AR (as in Hughes et al., 2015) correlation matrices and all analyses produced broadly comparable results. Task choice (hard versus easy) was the dependent variable and a repeated measures binary logistic distribution was used to model the probability of choosing the hard task. As the minimum number of trials completed by all participants was 44, we only considered this number of trials for our analysis. This is in keeping with previous work (e.g. Treadway et al., 2009; Hughes et al., 2015). All models included the significant predictors of probability, reward and expected value as predictors.

2.2.3.3.2 LFA

LFA was calculated in the same manner as previous studies (e.g. Pizzagalli, Sherwood, Henriques & Davidson, 2005; Boksem, Smolders & De Cremer, 2012). Alpha power indices were extracted for each electrode channel. In line with previous research, e.g. Hughes et al. (2015) we focused on 12 electrodes to calculate frontal (F3, F4, F5, F6), central (C3, C4, C5, C6) and posterior (P3, P4, P5, P6) asymmetry values. All values were log-transformed to correct for positive skew. Asymmetry scores were calculated by subtracting alpha power at the left hemisphere sites from their homologues on the right hemisphere, e.g. F4 – F3. A composite asymmetry index was then obtained by combining the asymmetry scores from the two pairs of sites at each location, e.g. LFA = [(F4-F3) + (F6-F5)]. Figure 2.2 illustrates the electrodes selected for analysis. This procedure was repeated for central and posterior sites, so that central alpha (CA) = [(C4-C3) + (C6-C5)] and posterior alpha (PA) = [(P4-P3) + (P6-P5)]. As alpha power is inversely related to cortical activity (Laufs et al., 2003), *greater* alpha activity in one hemisphere (as compared to the other) indicates *lower* tonic cortical activity in that hemisphere.

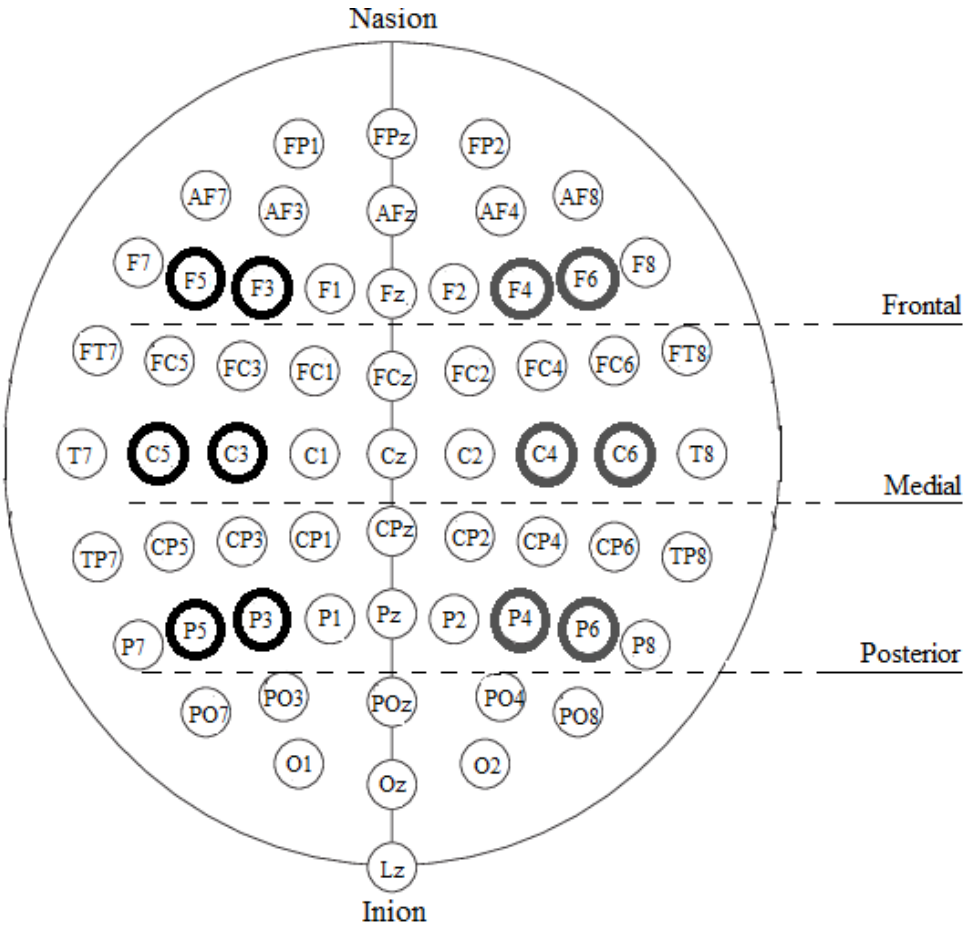

Figure 2.2: Topographical map of the electrode placements. Electrodes of interest are circled in bold on both hemispheres.

Separate asymmetry scores were obtained for the eyes open and eyes closed conditions and a 2 x 3 repeated measures ANOVA was carried out to check for main effects of eye condition, taking eye condition (open, closed) and cortical region (frontal, central and posterior) as the factors. No significant main effect of eye condition was observed (F (1, 45) = 2.37, p = .131), suggesting that results were similar across both conditions. Thus, both conditions were combined for each participant to provide a more robust estimate of asymmetry. Cronbach's alpha for asymmetry measures was high (frontal asymmetry α = .75; medial asymmetry α = .75; posterior asymmetry α = .80), suggesting that the pairs of homologous sites at each region were providing consistent estimates of alpha power.

2.3 Results

2.3.1 Descriptive Statistics

2.3.1.1 Self report measures and EEG variables

The means and standard deviations for all relevant self-report and EEG variables are presented in table 2.1. Correlations between individual self-report measures were assessed and these are summarised in table 2.2. The alpha threshold, corrected for multiple comparisons, = 0.005 (0.05/10). Moderate correlations were observed between discrete measures of anhedonia, e.g. SHAPS and TEPS ANT (r = .424, p =.002), and between approach motivation and anhedonia, e.g. TEPS Total and BAS (r = .426, p = .002). The reward responsiveness subscale of the BAS (BAS RR) showed a slightly stronger relationship with TEPS ANT (r = .523, $p < 0.01$) than did the BAS total (r = .482, $p < 0.01$). Finally, the BDI-II was inversely related to the SHAPS (r = -.468, p = 0.001).

Unexpectedly, no significant correlations were observed between LFA and any of the self-report measures of anhedonia, depression or approach motivation. Similarly, no significant relationships were observed between the self-report measures and the asymmetry indices at central or posterior site (see table 2.2).

Table 2.1: Means and standard deviations of self-report and EEG variables.

	Mean	SD
SHAPS (total)	47.38	6.25
TEPS (total)	78.65	12.96
TEPS ANT	42.33	9.01
TEPS CON	36.33	6.62
BAS (total)	41.62	4.87
BAS RR	17.90	1.94
BDI-II	9.35	8.11
LFA	0.09	0.21
LCA	0.197	0.19
LPA	0.25	0.33

Table 2.2: Correlations between self-report measures and EEG variables

	SHAPS	TEPS	TEPS ANT	TEPS CON	BAS	BAS RR	BDI II	LFA	CA
TEPS	.380 .005								
TEPS ANT	.424* .002	.887* .000							
TEPS CON	.188 .186	.769* .000	.388 .005						
BAS	.151 .291	.426* .002	.482* .000	.184 .196					
BAS RR	.167 .240	.505* .000	.523* .000	.285 .043	.672* .000				
BDI II	-.468* .001	-.220 .121	-.211 .137	-.147 .304	.102 .478	.068 .634			
LFA	.266 .070	-.102 .494	-.086 .565	-.077 .607	.015 .920	-.068 .652	-.086 .564		
LCA	.251 .089	-.224 .131	-.194 .191	-.162 .278	-.219 .140	-.159 .286	-.169 .256	.282 .055	
LPA	.080 .596	.061 .685	.126 .402	-.043 .774	-.056 .709	.035 .817	-.275 .065	-.348 .018	.231 .123

* Correlation is significant after adjustment for multiple comparisons ($\alpha = 0.05/10 = 0.005$).

Note: SHAPS = Snaith Hamilton Pleasure Scale; TEPS = Temporal Experience of Pleasure Scale; TEPS ANT = anticipatory subscale of the TEPS; TEPS CON = Consummatory subscale of the TEPS; BAS = Behavioural Approach scale of the BIS / BAS Scales; BAS RR = Reward Responsiveness subscale of the BAS; BDI II = Beck Depression Inventory II; LFA = Left frontal asymmetry; LCA = Left central asymmetry; LPA = Left posterior asymmetry.

2.3.1.2 Effort Expenditure for Rewards Task (EEfRT)

A mix of easy and hard task choices were made by all participants. At least 93% of all trials were completed during the 20-minute period of play. The proportion of hard task choices varied across all levels of probability, so that the hard task was chosen on 21.4% of low probability (12%) trials, 47.5% of medium probability (50%) trials, and 62.14% of high probability (88%) trials. Reward magnitude (i.e. the monetary value of the reward, where high reward is greater than £3.05; medium reward ranges from £2.01 to £3.04 and low reward is less than £2.00) predicted a significant difference on willingness to choose the hard task (t (1, 51) = - 17.41, $p < .001$), so that the hard task was chosen on 91% of high probability, high reward trials (i.e. where the likelihood of

reward receipt was 88% and the reward magnitude > £3.05), but only 29% of high probability, low reward trials (i.e. where the likelihood of reward delivery was 88%, but the reward magnitude was < £2.00). Table 2.3 shows the correlations between the mean hard task choices for each level of probability with the other variables. Only the correlation between LFA and hard task choice for the low level of probability (12%) was significant (r = .332, p = .026) and this relationship did not survive correction for multiple comparisons (α = 0.005, i.e. 0.05 / 10).

Table 2.3: Correlations between mean hard task choices for each level of probability with self-report measures and LFA

	Mean Hard Task Choices		
	Low (12%)	Medium (50%)	High (88%)
LFA	.326 .026	.110 .463	-.059 .694
LCA	.106 .479	-.006 .971	-.111 .459
LPA	-.033 .827	-.197 .189	-.063 .677
TEPS ANT	.048 .740	-.126 .377	-.060 .674
TEPS CON	-.023 .871	-.121 .397	-.036 .801
TEPS TOTAL	.021 .882	-.148 .299	-.060 .674
BAS	.115 .423	.016 .909	-.055 .703
BAS RR	.061 .668	-.152 .286	.045 .754
SHAPS	-.044 .596	.014 .921	-.039 .785
BDI II	-.026 .855	.118 .411	.097 .500

Note: Corrected for multiple comparisons, α = 0.005 (0.05 / 10).

2.3.2 Main Analyses: Generalised Estimating Equations

A preliminary GEE model examined the effects of trial number, probability of reward receipt, reward magnitude and expected value (probability x reward magnitude). This model, summarised in table 2.4, indicates that all four parameters were independent

predictors of choosing the hard task. Thus, the size of the reward available (reward magnitude), the likelihood of receiving the reward (probability), the expected value (i.e. reward magnitude x probability) and the position of the trial in the sequence of 44 trials, all significantly predicted how likely participants were to choose to expend additional effort for the reward. This is in line with all previous studies using the EEfRT (e.g. Geaney et al., 2015; Hughes et al., 2014; Treadway et al., 2009). These variables were included in all subsequent models with additional predictors added to investigate the main hypotheses, i.e. whether anhedonia and LFA would predict choosing the hard task.

Table 2.4: GEE models 1 to 3 assessing the likelihood of choosing the hard task considering the task parameters and the LFA scores.

				95% CI		
	Predictor	*b*	SE	Lower	Upper	*p*
Model 1						
	Trial	-.027	.003	-.034	-.020	.000
	Probability (12)	1.042	.429	.201	1.882	.015
	Probability (50)	.521	.214	.102	.941	.015
	Magnitude	.350	.110	.012	.021	.000
	Expected Value	.017	.002	.021	52.79	.000
	Predictor	*b*	SE	Lower	Upper	*p*
Model 2						
	Trial	-.028	.003	-.036	-.021	.000
	Probability (12)	1.099	.472	.175	2.023	.020
	Probability (50)	.511	.234	.053	.970	.029
	Magnitude	.356	.112	.137	.575	.001
	Expected Value	.017	.003	-.012	.022	.000
	LFA	1.00	.721	-.412	2.41	.165
Model 3						
	Trial	-.028	.004	-.036	-.021	.000
	Probability					
	Low (12%)	.684	.562	-.418	1.785	.224
	Medium (50%)	.394	.244	-.084	.871	.106
	Magnitude	.361	.118	.130	.592	.002
	Expected Value	.017	.003	.012	.022	.000
	LFA	-.344	.706	-1.727	1.040	.629
	LFA*probability					
	Low (12%)	3.075	1.09	.939	5.21	.005
	Medium (50%)	.964	.679	-.367	2.29	.156

Model 2 included LFA as a predictor of choosing the hard task. This term was non significant (b = 1.00, p = .165). Model 3 tested for interactions between LFA and the probability of reward receipt (i.e. Low = 12%; Medium = 50%; High = 88%). This interaction indicated that LFA was a significant predictor of hard task choice only when likelihood of reward delivery was low (12%) relative to when it was high (88%) (b = 3.075, p = .005), which was in-line with our predictions. This finding remains significant after correction for multiple comparisons (α = .007, i.e. 0.05 / 7).

Table 2.5: GEE models 4 and 5 assessing the likelihood of choosing the hard task considering the task parameters and the TEPS.

				95% CI		
	Predictor	*b*	SE	Lower	Upper	*p*
Model 4						
	Trial	-.027	.004	-.034	-.020	.000
	Probability					
	Low (12%)	1.043	.431	.200	1.89	.015
	Medium (50%)	.522	.215	.101	.943	.015
	Magnitude	.352	.111	.135	.569	.001
	Expected Value	.017	.002	.012	.021	.000
	TEPS ANT	-.002	.015	-.031	.028	.920
	TEPS CON	-.016	.023	-.060	.028	.481
Model 5						
	Trial	-.027	.004	-.034	-.020	.000
	Probability					
	Low (12%)	.477	1.466	-2.39	3.35	.745
	Medium (50%)	1.09	.959	-.785	2.98	.253
	Magnitude	.354	.112	.135	.573	.000
	Expected Value	.017	.002	.012	.021	.000
	TEPS ANT	-.005	.017	-.038	.029	.784
	TEPS CON	.010	.024	-.057	.036	.663
	TEPS ANT * probability					
	Low (12%)	.018	.029	-.038	.075	.522
	Medium (50%)	-.006	.021	-.046	.035	.782
	TEPS CON * probability					
	Low (12%)	-.006	.038	-.081	.069	.878
	Medium (50%)	-.009	.026	-.059	.041	.721

Contrary to expectations no main effect of anhedonia was observed for self-reported anticipatory hedonic tone (TEPS ANT: b = -.002, p =.920; see model 4) nor for reward responsiveness, measured by BAS RR (b = .037, p = .630; see model 6). Unsurprisingly, the consummatory measures of anhedonia, TEPS CON (b = -.016, p =.481; see model 4) and SHAPS (b = -.015, p =.826; see model 6), also did not predict hard task choice on the EEfRT.

All self-report measures were examined for interactions with the task parameter probability, as we expected that the likelihood of reward receipt would interact with self-reported measures of anhedonia and approach motivation to predict choice of the hard task. We hypothesised that this relationship would be strongest for the low likelihood of reward receipt (i.e. 12%) relative to the high probability of reward (88%) condition. Contrary to expectation, no significant interactions were observed for the TEPS ANT with either the contrasts for the low (12%; relative to high, 88%) (b = -.018, p =.522) or the medium (50%; relative to high, 88%) (b = -.006, p = .782) probability of reward delivery (see model 5). Similarly, no significant interactions were noted between the BAS RR and either the low (b = .088, p = .438) or medium (b = -.094, p = .175), relative to high, probability conditions (see model 7). Finally, as expected, measures of consummatory anhedonia TEPS CON and SHAPS, did not interact with the probability of reward receipt to predict willingness to expend effort for reward (model 5 in table 2.5 and model 7 in table 2.6, respectively).

Table 2.6: GEE models 6 and 7 assessing the likelihood of choosing the hard task considering the task parameters, the SHAPS and the BAS RR.

				95% CI		
	Predictor	*b*	SE	Lower	Upper	*p*
Model 6						
	Trial	-.027	.004	-.034	-.020	.000
	Probability					
	Low (12%)	.318	.533	-.727	1.362	.551
	Medium (50%)	.202	.249	-.286	.690	.417
	Magnitude	.351	.111	.134	.567	.002
	Expected Value	.017	.002	.012	.021	.000
	SHAPS	-.004	.019	-.041	.033	.826
	BAS RR	.021	.061	-.099	.142	.727
Model 7						
	Trial	-.027	.004	-.034	-.020	.000
	Probability					
	Low (12%)	-.950	3.117	-7.060	5.159	.760
	Medium (50%)	1.139	1.749	-2.288	4.567	.515
	Magnitude	.536	.139	.263	.809	.000
	Expected Value	.013	.003	.008	.018	.000
	SHAPS	-.010	.021	-.051	.031	.636
	BAS RR	.037	.076	-.113	.187	.630
	SHAPS * probability					
	Low (12%)	-.007	.040	-.086	.072	.862
	Medium (50%)	0.016	.022	-.027	.058	.475
	BAS RR * probability					
	Low (12%)	.088	.113	-.134	.310	.438
	Medium (50%)	-.094	.069	-.230	.042	.175

2.4 Discussion

The goal of the current study was to investigate the relationships between different measures of approach motivation: The EEfRT, a behavioural measure; LFA, a putative neural index; and several questionnaire measures: The TEPS, the SHAPS and the BAS sub-scale of the BIS / BAS scales. We hypothesised that LFA would be associated with a greater number of hard task choices on the EEfRT and that this association would be strongest for those trials on which participants had a low probability of receiving a

reward (i.e. 12% probability trials). We also hypothesised that the anticipatory subscale of the TEPS (TEPS-ANT) and the reward responsiveness subscale of the BAS (BAS RR) would predict willingness to expend effort for reward, in contrast to measures of consummatory pleasure, e.g. the SHAPS and the consummatory subscale of the TEPS (TEPS-CON). Again, we expected this finding to be most pronounced for low probability trials.

Our hypotheses were only partially supported. While no main effect of LFA was observed to predict hard task options on the EEfRT, our analyses yielded a significant interaction between LFA and probability of reward receipt (model 3), suggesting that LFA significantly predicted likelihood of choosing the hard task when the probability of reward receipt was low (12%) relative to high (88%), after correcting for multiple comparisons. Subsequent models (4 – 7) tested the utility of the psychometric measures as predictors of hard task choice. Contrary to predictions, these measures did not significantly predict hard task choice in any instance, nor did they reveal any interactions with the probability of reward delivery. While this outcome was expected for measures of consummatory pleasure (i.e. the TEPS CON and SHAPS), it was unexpected for measures of anticipatory pleasure and reward responsiveness (i.e. the TEPS ANT and BAS-RR).

In keeping with all previous published research utilising the EEfRT, the main task parameters of reward magnitude, reward probability, trial and expected value (magnitude x probability) were significant predictors of choosing the hard task (e.g. Bryant et al., 2017; Hughes et al., 2015; McCarthy et al., 2015; Treadway et al., 2009; Wardle et al., 2012). This reinforces the utility of the EEfRT and suggests the task worked as anticipated in the present sample, so that participants were more likely to choose the hard task to obtain higher rewards and / or when the receipt of reward was most likely. Participants were less likely to choose the hard task as they progressed through the task; a common finding, typically attributed to fatigue (e.g. Treadway et al., 2009; Hughes et al., 2015). Performance on the EEfRT was also comparable to that of other samples, with 91% of high reward / high probability combinations resulting in a hard task choice (similar, e.g. to the 94% observed by Hughes et al., 2015), and a minimum of 44 trials played by all participants (similar, e.g. to the 47 minimum trials reported by Treadway et al., 2009). Thus, the absence of a main effect of LFA in this

sample cannot be attributed to idiosyncrasies in participants' performance on the EEfRT.

This absence of a significant main effect between LFA and hard task choice was surprising, given that this finding was previously observed by Hughes et al (2015) and considering the wide body of literature implicating LFA as an index of approach motivation (see reviews by Harmon-Jones & Gable, 2017; Reznik & Allen, 2017; Kelley, Hortensius, Schutter & Harmon-Jones, 2017, but see also a meta-analysis by Wacker, Chavanon & Stemmler, 2010, suggesting such findings are less consistent than typically assumed). It is worth noting, however, that few previous studies have considered LFA in relation to a *behavioural* measure of reward motivation; rather, most studies assess LFA in relation to psychometric measures of approach motivation and reward processing. Notable exceptions to this trend are studies by Hughes et al. (2015) and Pizzagalli, Sherwood, Henriques and Davidson (2005), both of whom report significant relationships between LFA and behavioural tasks assessing motivation for reward. Similar to Hughes et al. (2015), we identified a positive interaction between LFA and probability on the EEfRT (although, contrary to the present study, Hughes et al. also observed a significant main effect of LFA). This effect was significant only for the low (relative to high) probability trials, i.e. when the contrast between likelihood of receiving a reward was greatest. Interpretation of this finding is in keeping with the view that dopamine drives a greater willingness to engage in effortful activity to obtain rewards, especially in circumstances where individuals are less likely to receive the reward. Support for this argument comes from previous work in the animal literature associating the firing of accumbens dopamine neurons with probabilistic values of reward receipt (Fiorillo Tobler & Schultz, 2003; Niv, Duff & Dayan, 2005; Tobler, Fiorillo & Schultz, 2005), so that the greatest level of dopaminergic function is observed when reward receipt is most unlikely or uncertain. Reward receipt was most unlikely for the low (relative to high) contrast in the present study. Thus, we suspect that LFA reflects left-lateralized engagement of dopaminergic processes in frontal areas, in-keeping with findings from Treadway et al. (2012b) and Wacker et al. (2013).

It is unclear why a significant interaction was not also observed for the contrast between medium (50%) relative to high (88%) probability of reward receipt. The limited existent human literature reports mixed findings about the relationship of putatively

dopaminergic processes, such as ECDM and the influence of the likelihood of reward receipt. Wardle et al. (2011) found evidence to suggest administration of a *d*-amphetamine (i.e. a drug that increased levels of extracellular dopamine) increased participants' selection of the hard task on the EEfRT in both the low (12%) and medium (50%) probability trials (but did not affect the influence of reward magnitude). Thus, *d*-amphetamine is thought to increase willingness to expend effort for reward via increased extracellular levels of dopamine, irrespective of the reward value. In contrast, Treadway et al. (2012b) reported that greater D_2 and D_3 receptor availability in the bilateral vmPFC, left vlPFC, the left caudate and the left inferior temporal gyrus, was associated with choice of the hard task on the EEfRT; a finding that was particularly strong for the low (12%) relative to high (88%) contrast. Most recently, Ohmann, Kuper & Wacker (2018) reported an interaction between stimulation of the left dlPFC using anodal tDCS and the probability of reward receipt on the EEfRT. This relationship was associated with a greater number of hard task choices for low (12%) relative to high (88%) probability trials, but no comparable relationship was observed for low relative to medium (50%) probability trials, which provides some support for the results of the present study. Taken together, these converging research paradigms present a tentative step forward in our understanding of approach motivation. It is clear that most healthy people are likely to choose to expend (physical) effort for a reward if it is relatively easy or if they are likely to obtain it. In contrast, only those individuals with greater LFA, more sensitive dopaminergic receptors – particularly in left frontal regions – or who have had their dopaminergic system sensitized (e.g. through the administration of amphetamine) are willing to pursue relatively unlikely rewards. Based on the evidence from Treadway et al. (2012b) and Ohmann, Kuper and Wacker (2018), the left frontal cortex seems uniquely implicated in this ECDM, providing some support for – and further specification of – Davidson's (1992) and Gray's (1972) theories about the neural bases of behavioural approach.

As previously noted, much of the prior research in this area investigates LFA in relation to self-report measures of reward responsivity and approach motivation. In particular, such work has sought to correlate LFA with Carver & White's (1994) BIS / BAS scales. Early, often-cited work illustrates this relationship, e.g. both Sutton and Davidson (1997) and Harmon-Jones & Allen (1997) found that participants who scored higher on the BAS subscale also had relatively higher LFA (i.e. relatively greater left than right

cortical activity) in the alpha band. However, replication of these findings has proven controversial, e.g. Wacker, Chavanon and Stemmler (2010) found no significant correlation between BAS and LFA in the alpha band in four independent studies and a further meta-analysis indicated no reliable association between frontal asymmetry and BAS / alternative measures of agentic extraversion (an analogous concept to the behaviour approach system, coined by Depue and Collins, 1999). Given these latter findings, it is perhaps unsurprising that the current study found no significant relationship between LFA and BAS RR.

Contrary to the conclusion of Wacker, Chavanon and Stemmler (2010), we suggest inconsistencies in these findings may, in part, be due to issues with the psychometric properties of the BIS / BAS scales themselves. Research in this area typically combines all three sub-scales of the BAS for analysis in relation to LFA (e.g. Hughes et al., 2015). We argue that this is conceptually problematic, given work by Heym, Ferguson and Lawrence (2008), which indicates that the reward responsiveness subscale of the BAS (BAS RR) is uniquely associated with motivation to persevere to obtain a reward, whereas the total BAS score conflates this with other subscales, assessing different reward processing facets, e.g. fun-seeking / impulsivity. Heym, Ferguson and Lawrence (2008) emphasise that the uniformity of BAS is questionable, given differential relationships between the fun-seeking (BAS-FS) and reward responsivity (BAS-RR) subscales with Eysenck's conceptualisations of Psychoticism, Extraversion and Neuroticism (Eysenck & Eysenck, 1985). She illustrates this by suggesting that these subscales may exert suppressor effects on one another, due to the opposing nature of the directional relationships between BAS-RR and BAS-FS with the PEN. Such suppressor effects may partly explain why BAS does not always yield a relationship with LFA, e.g. all ten studies using the BAS in the Wacker, Chavanon and Stemmler (2010) meta-analysis use a total BAS score. As this accounts for almost half of the total number of studies entered into the meta-analysis, it is possible that the use of the total BAS score is undermining the utility of LFA as an index of approach motivation.

To counter this issue, we focused on the BAS-RR subscale in the present study. Unexpectedly, no relationships were observed between the BAS-RR and the EEfRT, either among the correlational relationships or in the main (GEE) analyses. To our knowledge, this is the first study to specifically consider the relationship between BAS-

RR and the EEfRT or, indeed, between BAS-RR and LFA. The absence of a significant relationship between BAS-RR and EEfRT is surprising. Geaney, Treadway and Smillie (2015) note a significant interaction between the total BAS scale and the probability of reward receipt on the EEfRT, so that participants with higher total scores on the BAS were more likely to choose the hard task on the EEfRT when reward receipt was most unlikely (i.e. 12% compared with 88%). In light of the argument by Heym, Ferguson and Lawrence (2008), that use of the total BAS score likely leads to suppressor effects between the BAS-RR and BAS-FS subscales, we expected to observe a stronger relationship with the probability parameter of the EEfRT when using the BAS-RR subscale (rather than the total BAS score). Recent work by Johnson, Swerdlow, Treadway, Tharp and Carver (2017) report an influence of the Willingly Approached Set of Statistically Unlikely Pursuits (WASSUP; Johnson & Carver, 2006) on the EEfRT in a group of patients with Bipolar Disorder. The WASSUP assesses practical analogues of the BAS; the likelihood that participants will set life goals that are hard to achieve, e.g. appearing on TV regularly or a high income threshold, but with an emphasis on goal setting, rather than goal persistence (as in the BAS-RR). Johnson et al. (2017) observe an interaction between the financial success subscale of the WASSUP and the reward magnitude parameter on the WASSUP, so that higher scores were linked to a greater number of hard task choices, when reward magnitude was low (~$1.24) relative to high (~$4.30). Thus, it may be that the relationship observed by Geaney, Treadway and Smillie (2015) between EEfRT and BAS was driven, not by the reward responsiveness scale, as assumed in the present study, but by an alternative aspect of the BAS, e.g. BAS-drive, which relates to goal-directed behaviour. Further work is needed to clarify this association and, preferably, such work should focus on newer self-report measures of the RST (e.g. Reuter, Cooper, Smillie, Markett & Montag, 2015; Corr & Cooper, 2016), which accurately reflect the revised RST.

The failure of any of the self-report measures to predict performance on the EEfRT is surprising, given that these measures are ostensibly assessing similar concepts. This finding is not in keeping with prior literature, which typically indicates that both the total score and the anticipatory sub-scale of the TEPS are predictive of performance on the EEfRT, for both healthy controls and depressed patients (though not for patients with remittent depression; Yang et al., 2014). Geaney et al. (2015) report a predictive role for both TEPS-ANT and BAS (total scores) on EEfRT performance. Specifically,

higher scores on the TEPS-ANT and BAS-TOTAL predict willingness to choose the hard task when the probability of reward receipt is low (12%) relative to high (88%). The existent literature considering both the TEPS and the EEfRT in combination is too scare to make firm conclusions about the absence of a significant relationship in the present study. Using an alternative measure of anhedonia, the Specific Loss of Interest and Pleasure Scale (SLIPS; Winer, Veilleux & Ginger, 2014), recent work by Bryant, Winer, Salem and Nadorff (2017) suggests that the relationship between anhedonia and effort expenditure for reward may be more complex than traditionally assumed. Using a negative mood induction paradigm, they examined whether action orientation would act as a buffer between levels of anhedonia and performance on the EEfRT among healthy controls. Action orientation refers to an individual's ability to upregulate positive affect to enable goal pursuit, particularly when an individual is experiencing high negative affect. Results from this work suggest that action orientation may act as a buffer against anhedonia in the pursuit of rewards, when anhedonia is experienced at low levels. However, at high levels of anhedonia, no protective influence of action orientation is observed, suggesting that individuals experiencing recent high-level increases in anhedonia are unable to upregulate their positive affect to pursue goals. Given the absence of a main effect of TEPS ANT on EEfRT in the study by Geaney et al. (2015), it is evident that factors other than anhedonia are influencing willingness to expend effort for reward. Thus, it is possible that the relationship between anhedonia, as measured by the TEPS, and ECDM, as measured by the EEfRT, is more nuanced than previously believed, and may be mediated by several other person variables.

In contrast, the absence of a relationship between hard task choice on the EEfRT and either of the consummatory measures of anhedonia (i.e. the SHAPS and the TEPS CON) was expected, based on the theoretical conceptualisation of ECDM as part of the anticipatory phase of reward processing. The absence of a relationship between the SHAPS and performance on the EEfRT echoes most prior work, e.g. Treadway et al. (2009) report no significant correlations between scores on the SHAPS and choice of the hard task on the EEfRT at any level of probability of reward receipt (i.e. 12%, 50% or 88%). Similarly, Geaney, Treadway and Smillie (2015) observed no predictive role for the SHAPS in relation to performance on the EEfRT (model 6 in Geaney, Treadway & Smillie, 2015), irrespective of level of probability (model 7), magnitude of the reward available (model 7) or the expected value of the reward (i.e. the multiplication of the

probability value by the reward magnitude; model 9). Similar to Treadway et al. (2009), they also found no significant correlational relationships between SHAPS scores and hard task choices on the EEfRT at any level of probability. One notable exception to this trend is work by Yang et al. (2014), who report a significant relationship between scores on a Chinese translation of the SHAPS (Liu, Wang, Zhu, Li & Chan, 2012) and hard task choices on the EEfRT for participants with remitted depression, when reward receipt was least likely (20%). Based on the information provided by the paper, however, this relationship would not survive correction for multiple comparisons. Similarly, no predictive role for the TEPS CON was observed in relation to any of the parameters of the EEfRT by Geaney, Treadway and Smillie (2015), reflecting the absence of a relationship between the TEPS CON and hard task choice on the EEfRT observed in the present study. Taken together, this work suggests that ECDM on the EEfRT does not appear to be linked to consummatory pleasure, as assessed by existent self-report measures of anhedonia.

Alternatively, the absence of any relationship between these self-report measures and ECDM on the EEfRT may be explained by attributes of the self-report measures themselves. As outlined in section 2.1.1, anhedonia may arise as a result of individual differences in reward processing in one of a number of areas, including ECDM. It may be that self-report measures, as relatively blunt instruments, are simply not sensitive enough to pick up individual differences in ECDM, such as those measured by the EEfRT (see McCabe, 2018 for further discussion on this topic). This argument points to a need for a new self-report measure of anhedonia, that is sensitive to the constellation of reward processing facets implicated in anhedonia. Chapter 4 outlines an attempt at creating one such measure and the Dimensional Anhedonia Rating Scale (DARS; Rizvi, Quilty, Sproule, Cyriac, Bagby & Kennedy, 2015) represents an alternative such measure. Neither of these scales have yet been used in conjunction with the EEfRT, but doing so represents a fruitful area for future work.

Finally, it should be noted that the factor structure of the TEPS has previously been called into question. A confirmatory factor analysis (CFA) of the TEPS by Ho, Cooper, Hall and Smillie (2015) indicated weak support for the two-factor structure of anticipatory and consummatory pleasure. This was largely due to the inter-correlation of items across both scales, indicating poor ability for these items to distinguish

between anticipatory and consummatory pleasure. Subsequent work by Garfield, Cotton and Lubman (2016) also suggests weak support for the two-factor structure and an inability to distinguish between consummatory and anticipatory pleasure in a sample of opioid-dependent participants. These critiques of the TEPS factor structure undermine its unique selling point in the literature, i.e. as a measure capable of differentiating between temporal experiences of pleasure. Viewed in light of this work, the absence of a significant relationship between performance on the EEfRT and the TEPS ANT may tentatively be taken as further evidence against the convergent validity of the TEPS.

This criticism of the convergent and divergent validity of the TEPS gleans some support from the pattern of correlations between the self-report measures in the present study. In particular, a small to moderate correlation was observed between the SHAPS and the TEPS ANT, but not the TEPS CON. Though surprising given the consummatory focus of the items in the SHAPS, this result is in keeping with a similarly-sized relationship between TEPS ANT and SHAPS reported by Geaney et al. (2015). Contrary to their findings, however, we observed no significant correlation between TEPS CON and the SHAPS in the present sample. This reflects a negligible relationship observed between the TEPS CON and the SHAPS by Ho et al. (2015). In-keeping with previous research, BAS showed a moderate correlation with the anticipatory sub-scale of the TEPS (TEPS ANT), but not with the consummatory sub-scale (TEPS CON) (Geaney et al., 2015; Gard et al., 2006; Ho et al., 2015), which was slightly stronger for the BAS-RR than the total BAS, likely reflecting the suppressor effects of the BAS subscales discussed by Heym, Ferguson and Lawrence (2008).

At the time of design, no studies had been carried out assessing the relationship between the TEPS and LFA. To our knowledge, two studies have subsequently assessed this relationship with mixed results. Similar to the present study, Liu, Sarapas & Shankman (2016) found no significant relationship between LFA and either sub-scale of the TEPS. They attributed this absence of effect to the trait-like nature of the TEPS, whereas resting state EEG may be subject to state effects, e.g. as in the study by Wacker et al. (2013), in which individual differences in LFA were only observed when participants were engaged in an approach motivated state. This reflects a larger debate over the precise nature of frontal alpha asymmetry in motivation (see, for example, Coan &

Allen, 2003; 2004; Reznik & Allen, 2017). Liu et al. (2016) also posit that specific aspects of anhedonia, such as interest or motivation, may selectively drive their observed association between melancholia and EEG asymmetry during anticipation of reward. As noted above, such aspects are traditionally overlooked by current measures of anhedonia, which tend either to focus on one domain of anhedonia (e.g. consummatory pleasure; the SHAPS) or distinguish only between temporal domains, e.g. anticipation and consummation, as in the TEPS, or social versus physical aspects, e.g. the Chapman scales for Physical and Social Anhedonia (Chapman, Chapman & Raulin, 1976). Thus, as discussed in relation to the EEfRT, existent self-report measures of anhedonia, may be insufficiently nuanced to pick up on individual differences in neural or behavioural measures of reward processing.

In contrast, Katz, Sarapas, Bishop, Patel and Shankman (2015) found that left frontal asymmetry significantly predicted TEPS-CON scores in the consummatory phase of an associative-learning reward task in the form of a slot-machine, comprising win, lose and no incentive parameters broken into two phases: anticipatory and consummatory (see Shankman, Klein, Tenke & Bruder, 2007), but did not predict scores on the TEPS-ANT during the anticipatory phase of the same task. This study, similar to that by Wacker et al. (2013), assessed LFA while participants were actively engaged in an approach motivated task. Taken together, this research raises the possibility that the absence of a relationship between LFA and measures of approach motivation in the present study may be attributable to the absence of a state-manipulation. Adherents of a LFA as a trait-like measure, typically point to studies citing acceptable ranges of test-retest reliability comparable to those found with questionnaire measures of personality. For example, Jones, Field, Davalos and Pickens (1997) report stability in alpha asymmetry from the age of three months to three years (r = .66); Winegust, Mathewson and Schmidt (2014) report similar re-test reliability, citing an intraclass correlation (ICC) of .57 in healthy adults over a period of one month; Allen, Urry, Hitt and Coan (2004) observed modest stability in a population of women diagnosed with MDD over a period of 8 to 16 weeks, with median ICCs of .56 (referenced to the average), .76 (referenced to Cz) and .41 (linked mastoid references). Finally, work by Hagemann, Hewig, Seifert, Naumann and Bartussek (2005) assessed resting state stability in healthy participants on three separate occasions, each session separated by five weeks. Using a latent trait-state structural equation model, they concluded that the frontal alpha

asymmetry score comprised approximately 60 per cent temporally stable, consistent individual differences (i.e. trait-like effects), while approximately 40 per cent of the variance was due to situational effects or interactions between the person and the situation (i.e. state-like effects). Thus, though some argument to support the trait-like aspects of LFA exist, it may be that these attributes are best observed when participants are engaged in an approach motivated state.

This debate over state influences on LFA highlights a core limitation of the present study. Namely, the resting state EEG was recorded after participants had completed the EEfRT. At this point, participants knew how much money they would receive (though they had not physically received the money). Thus, it is possible that satiation of reward wanting may have supressed putative state influences on the LFA. Work by Shankman, Sarapas and Klein (2011) lends credence to this idea; they report finding different patterns of frontal asymmetry in both clinically depressed participants and healthy controls prior to reward attainment compared to post reward receipt. Specifically, they observed greater left asymmetry in frontal regions in the alpha band before participants received a monetary reward, but greater right (relative to left) frontal alpha asymmetry following receipt of the reward. Thus, by informing participants of the amount of money "won" during the EEfRT, we may have inadvertently attenuated the LFA index.

The EEfRT itself has been subject to criticism for limitations in its design (see, e.g. Chong, Bonnelle & Husain, 2016; Hughes et al., 2015). Of relevance to the present study, it is possible that the hard task is less appealing to participants because it takes longer to complete (21 seconds compared to 7 seconds). While the temporal delay is brief, it is well-established that humans discount temporal delays in a hyperbolic manner, so that smaller rewards that are received sooner and preferred to larger, later rewards (Chong, Bonnelle & Husain, 2016). Given the widely reported significant effect of trial number on willingness to choose the hard task, it is likely that, contrary to popular thought, this may not reflect fatigue, but rather temporal discounting of rewards. Dissociation of these phenomena represents a challenge for future research.

Considering the literature and limitations discussed above, the measurement of approach motivation and anhedonia requires rethinking. Too few studies have attempted to triangulate measurement of approach motivation, using a combination of

behavioural, psychometric and neural paradigms. Thus, much of the literature has evolved in parallel, based on the assumption that these measures are assessing the same processes. Given the constellation and complexity of reward processing mechanisms - illustrated by the pre-clinical literature - and the growing interest in the role of reward-processing deficits in disorders such as depression and schizophrenia, as evidenced by the development of initiatives such as the Research Domain Criteria (RDoc), these assumptions need to be challenged and tested. The present research represents one of the first studies to investigate the role of LFA in relation to a behavioural measure of reward processing; the EEfRT. Building on previous work, e.g. by Hughes et al. (2015), we also considered the concurrent validity of psychometric measures of anhedonia. Ostensibly, LFA, as a neural index of approach motivation, anticipatory anhedonia and ECDM are similar concepts, which should be related to one another. Based on the present research, there is some tentative evidence supporting LFA as a neural predictor of willingness to expend physical effort for monetary rewards when the probability of reward receipt is maximally unlikely. The current study yields no evidence in support of convergent validity between either ECDM or LFA and psychometric measures of anhedonia, specifically the TEPS ANT, or broader measures of the behavioural approach system, BAS-RR.

A great swathe of existent work on LFA relies on linking this putative neural index of approach motivation to self-report measures of reward processing. In light of the literature discussed above, this is ill-conceived for several reasons: 1) A substantial proportion of this literature remains reliant on the BIS / BAS scales, an out-dated measure, which is not consistent with the revised Reinforcement Sensitivity Theory (Gray & McNaughton, 2000; see also Smillie, Pickering & Jackson, 2006). Future work on approach motivation should reconsider the use of the BIS / BAS or, at least report values for the three sub-scales independently, bearing in mind the potential suppressor effects posited by Heym, Ferguson and Lawrence (2008); 2) The validity of current self-report measures of anhedonia, particularly the anticipatory subscale of the TEPS, is also called into question by the present discussion. The debate over the psychometric properties of this measure (e.g. Ho et al., 2015) points to the need for further validation of this measure; 3) Given the broad array of reward processing deficits, which may present as a similar anhedonic phenotype, it is also likely that existent self-report measures, reliant as they are on one or two factors, may not be sensitive enough to

assess individual differences in, e.g. ECDM or similar sub-components of the reward cycle. Thus, this literature suggests the need to develop a broad measure of reward processing, which is sensitive to an array of sub-components of reward.

2.5 Conclusion

This study sought to contribute to the existing literature by examining the relationship between three measures of approach motivation: a behavioural measure, the EEfRT; a neural index, the LFA; and several psychometric measures, the TEPS-ANT and BAS-RR. As these measures purport to assess aspects of approach motivation, we expected to observe predictive roles for a) LFA; b) the TEPS-ANT; and c) the BAS-RR in choice of the hard task on the EEfRT. We excepted this relationship to be strongest under conditions when reward receipt was maximally unlikely (i.e. for the 12%, relative to 88% probability contrast). Results highlight an interaction between LFA and hard task choice on the EEfRT for the low (12%) relative to high (88%) probability of reward receipt, echoing previous research. The findings question the concurrent validity of both the TEPS and the BAS scales as measure of approach motivation, given the absence of any relationships between these measures and either the LFA or the EEfRT. Thus, these findings extend prior work by attempting to triangulate measurement of approach motivation using a combination of EEG, psychometric and behavioural measures.

Chapter 3

Cortical alpha asymmetry at posterior – but not anterior and central - sites is associated with individual differences in behavioural loss aversion.

Overview

Heightened sensitivity to losses, known as loss aversion, is a putative avoidance behaviour, which commonly influences decision-making, particularly in economic scenarios where participants have a 50/50 chance of winning or losing money. Evidence from neuropsychology, EEG and TMS research suggests individual differences in loss aversion may be explained by neural differences in the lateralisation of the right hemisphere. 40 healthy participants underwent an EEG recording during resting state and subsequently performed a behavioural loss aversion task, in which they had an equal chance of winning or losing money. EEG asymmetry in the alpha band at posterior sites – but not at anterior or central locations - was associated with individual differences in behavioural loss aversion. This asymmetry was driven by a combination of increased activation in the right hemisphere and decreased activation in the left hemisphere. Exploratory analyses sought to further characterise these data. These analyses revealed a non-significant correlation of 0.36 between central alpha asymmetry and the Flight sub-scale of the Jackson-5 (Jackson, 2009) revised reinforcement sensitivity questionnaire. In contrast, no role was observed for BIS (Carver & White, 1994) as a moderator of the relationship between cortical asymmetry and behavioural loss aversion. These findings are discussed in relation to the wider literature on behavioural withdrawal and anxiety.

3.1. Introduction

3.1.1 Behavioural loss aversion

Human decision making is subject to bias from a range of spurious influences, not least our personality traits and emotional states. Prospect theory (Kahneman & Tversky, 1979) attempts to account for some of these influences and, in turn, individual

differences in decision making. A key suggestion of this theory is that individuals are loss averse, that is, we overweight the negative impact of losses in comparison to the positive impact of gains. Research by Kermer, Driver-Linn, Wilson and Gilbert (2006) indicated that participants overestimated the negative impact of monetary loss on their mood both in the immediate aftermath of the loss and at a later time compared with actual variation in mood following a financial loss. In-keeping with this notion of loss aversion, most people will only accept a 50/50 financial gamble (i.e., a 50% chance of gaining or losing money) if the amount they stand to gain is at least twice as large as that they stand to lose (Kahneman, 2003).

Behavioural loss aversion is traditionally measured using a series of mixed gambles that vary in the magnitude of gains and losses (e.g., Tom, Fox, Trepel & Poldrack, 2007). Loss aversion is typically calculated by the mathematical parameter Lambda (λ), using the formula: $\lambda = -\beta_{loss} / \beta_{gain}$. Both β coefficient values are obtained from a logistic regression used to predict the decision made, with gain and loss amounts used as predicting variables. Studies of behavioural loss aversion typically report a λ with a mean value of 2, in-keeping with participants' double-weighting of losses compared to gains (Haigh & List, 2005; Heeren, Markett, Montag, Gibbons & Reuter, 2016; Johnson & Goldstein, 2003; Post, Van der Assem, Baltussen & Thaler, 2008; Tovar, 2009). However, slightly lower values have also been observed (e.g., Frydman, Camerer, Bossaerts & Rangel, 2011; Sokol-Hessener, Hsu, Curley, Delgado, Camerer & Phelps, 2009), potentially reflecting methodological variations in the choices offered to participants.

3.1.2 Loss aversion and the right hemisphere

Neuropsychology research supports the involvement of the right hemisphere in risky decision making, suggesting that individual differences in the neural functioning of the right hemisphere may underpin variation in behavioural loss aversion. Patients with acquired injuries to frontal brain areas tend to exhibit a preference for risky decisions with little regard for potential negative consequences, suggesting diminished or absent loss aversion (Rahman, Sahakian, Cardinal, Rogers & Robbins, 2001). This effect is pronounced for lesions to the right hemisphere, particularly in the right ventromedial prefrontal area (Clark, Manes, Antoun, Sahakian & Robbins, 2003; Tranel, Bechara &

Denburg, 2002). This involvement receives support from neuroscientific research by Knoch, Gianotti, Pascual-Leone, Treyer, Regard, Hohmann & Brugger (2006a), who found that healthy participants made riskier decisions on a gambling task after the application of transcranial magnetic stimulation (TMS) to disrupt the right dorsolateral prefrontal cortex (PFC). This effect was not observed when TMS was applied to the left dorsolateral PFC.

3.1.3 EEG alpha asymmetry and reward sensitive behaviour

Researchers have sought to characterise the source of loss aversion by considering how individual differences in neurobiological traits reflecting reward sensitivity can influence decision making. The hemispheric asymmetry of tonic prefrontal activity, assessed using resting-state electroencephalography (EEG), is thought to be a relatively stable index of behavioural approach and avoidance (Davidson, 2004; Harmon-Jones, Gable & Peterson, 2010; Tomarken, Davidson, Wheeler & Kinney, 1992). Tonic cortical activity is typically quantified by measuring the power of alpha-band (8-13 Hz) oscillations (see, e.g., Davidson, 1992). Alpha-band oscillatory activity reflects cortical hypoactivation (Coan & Allen, 2004), such that *greater* alpha power in one hemisphere (as compared to the other) indicates *lower* tonic cortical activity in the former (than in the latter). Thus, relative right frontal asymmetry is indicative of lower right (relative to left) alpha power, which signifies greater right (relative to left) cortical activation.

Greater left, relative to right, tonic activity in frontal regions is thought to reflect greater reward approach motivation, whereas greater right (relative to left) frontal activity is thought to reflect avoidance behaviours and disengagement (Davidson, 1992). This theory is grounded in evidence from neuropsychological cases of brain damage, wherein unilateral left-sided frontal lesions were more likely to lead to a 'catastrophic-depressive reaction' (Gainotti, 1969, 1972). These observations were bolstered by experimental evidence in which the left hemisphere was inactivated through the injection of intracarotid Amytal. Terzian and Ceccotto (1959) reported different emotional reactions in patients, depending on which hemisphere was inactivated: participants with an inactivated left hemisphere displayed a similar depressive response to those patients with left unilateral damage. In contrast, participants whose right hemisphere had been inactivated with Amytal, presented with a manic euphoric

reaction. Davidson considered this evidence in light of reports from the child development literature, which suggested that reaching and grasping behaviours, ostensibly linked to approach motivation, were typically initiated by the left hand in infancy, irrespective of the child's later handedness (e.g. Young, Segalowitz, Misek, Alp & Boulet, 1983). Taken together, Davidson suggested this evidence represented a basis for a generalised lateralisation of emotion / motivation, in which approach for rewards was left-lateralised and withdrawal from punishment was right-lateralised. By extension, he argued that decreased activation of the left cerebral hemisphere (relative to that of the right) placed an individual at an increased risk for the development of depression (reflecting the catastrophic depressive reaction observed by Gianotti and others). Conversely, a relative deficit in right (compared to left) activation left the individual vulnerable to the development of anxiety disorders. Davidson argued that this vulnerability could best be observed in the alpha band of an EEG recording at frontal sites.

These asymmetries have subsequently been linked to the biological processes underlying Gray's (1972) personality systems: the behavioural approach system (BAS), which is sensitive to reward and underlies motivation to approach rewards, and the behavioural inhibition system (BIS), which is sensitive to punishment or fear and can initiate avoidance behaviours (Davidson, 2004; Harmon-Jones, 2004; Sutton & Davidson, 1997). Although neither the original reinforcement sensitivity theory (RST; Gray, 1972), nor the revised version (Gray & McNaughton, 2000) consider hemispheric lateralisation of these processes, a great deal of research has considered frontal alpha asymmetries in relation to psychometric measures of reward sensitivity, particularly Carver and White's (1994) BIS/BAS scales. This link is based on similarities between the approach-related deficits observed in left-lateralised brain damage (discussed above) and the approach-related functions of the BAS, as described by Gray (1972). Notably, the lateralisation of withdrawal / avoidance behaviours to the right hemisphere has yielded less robust evidence (see Davidson, 1992) and the similarities between this system and the BIS (and subsequent Flight-Fight-Freeze System; FFFS) have been less clearly articulated.

In addition to the lack of clarity of this right lateralisation of avoidance / withdrawal behaviours, relatively little work has examined alpha asymmetry in relation to actual

reward-related behaviour (rather, work in this area tends to focus on self-report psychometric measures such as the BIS /BAS). Research that has considered reward-related behaviour has tended to focus on approach behaviour (e.g. Hughes, Yates, Morton & Smillie, 2015; Pizzagalli, Jahn & O'Shea, 2005) and little work has sought to characterise loss aversion specifically.

3.1.4 EEG asymmetry and avoidance behaviour in infancy

The developmental literature on attachment has consistently linked frontal EEG asymmetries to inhibited / avoidance behaviours in the face of novel / threatening stimuli (see Gander & Bucheim, 2015 for a review). Calkins, Fox and Marshall (1996) observed greater right (compared to left) frontal activation in 9 month olds, which was associated with increased inhibited exploratory behaviour at 14 months in a group of infants classified as high negative affect, compared to their high positive affect peers. Similarly, Hane, Fox, Henderson and Marshall (2008) found that four-month-old infants prone to negative reactions were more likely to show avoidance behaviour and reduced approach behaviour in the face of a fearful stimulus at 9 months, which was accompanied by a pattern of greater cortical activation at right (relative to left) frontal regions. Extending this work, Buss, Schumacher, Solski, Kalin, Goldsmith & Davidson (2003) report a link between avoidant behaviours (fear and sadness), relative right asymmetry (indicative of greater right cortical activation) and higher levels of both basal and reactive cortisol in 6-month old infants in response to a negative affect task.

3.1.5 Loss aversion and resting state EEG asymmetries

Given the above research, a link between loss aversion, a putative avoidance behaviour, and right frontal alpha asymmetry (i.e. greater right cortical activation) would be expected. However, research findings in this area have been mixed. Some research has identified a role for right (relative to left) PFC activity in individual risk taking behaviour. Specifically, Gianotti et al (2009) found that healthy participants with higher resting state activity, obtained during an EEG recording in the right (compared to the left) PFC showed lower levels of risk averse behaviour on a risk-taking task. This task, the 'devil's chest', offers participants an array of ten closed boxes, which must be opened sequentially. Nine of the ten boxes allow the participant to win money, but one

(randomly distributed) box contains a 'devil', which makes the participant lose all their money for that trial. Measured in this way, aversion to risk is generally thought to arise as a result of loss aversion (Kobberling & Wakker, 2005). Participants with greater aversion to loss will open fewer chests, as the odds of finding the 'devil' and losing all of one's winnings becomes greater as more chests are opened. Similarly, Studer, Pedroni & Rieskamp (2013) report a relationship between greater power in the right (relative to left) frontal regions in the theta band (4-7 Hz) of a resting-state EEG recording and increased risk-taking behaviour, suggesting diminished loss aversion. Interestingly, they also highlight a relationship between increased BIS scores and decreased risk taking behaviour. Work by Schutter and van Honk (2005), in contrast, has examined the relationship between disadvantageous decision making on the Iowa Gambling Task and the ratio between frontal low-frequency oscillations (indicating cortical inactivity) and high-frequency oscillations (indicating cortical activity) during resting state. While higher values of this frontal EEG ratio were associated with more disadvantageous decision making, this effect was global and was found across both hemispheres. Additionally, the ratio of low- to high-frequency oscillations over *posterior* cortical regions was most significantly associated with disadvantageous decision making. Finally, Telpaz & Yechiam (2014) found that individuals with stronger left- than right-hemispheric frontal activity showed increased risk-taking on a mixed gambling task, relative to participants characterised by stronger right than left tonic activity.

3.1.6 Hypotheses

Given the mixed findings represented by the above studies and the links between frontal asymmetry and withdrawal behaviour and punishment avoidance, we sought to investigate the relationship between cortical asymmetry and loss aversion. We predicted an association between rightward asymmetry, i.e., stronger tonic activity in the right as compared to the left hemisphere (reflected in lower right - relative to left - alpha power) and greater loss aversion, as assessed by the loss aversion parameter λ. We further hypothesised that this effect would be most pronounced in frontal regions, given the neuropsychological and neuroscientific evidence supporting the role of the right PFC in avoidance behaviours. Given the existent inconsistent reports on the

location of asymmetry indices, we also conducted an exploratory analysis to consider asymmetry values at central and posterior sites in relation to loss aversion.

3.2. Methods

3.2.1 Participants

N=41 healthy participants (23 female; mean age *M*=22.8 years, *SD*=4.33 years) volunteered their time in exchange for course credit. One participant was excluded due to excessive data loss during the EEG analysis, leaving a final *N*=40. All participants were free of past or present neurological or psychiatric disorders. Data from the same participants have previously been reported in Voigt, Montag, Markett & Reuter (2015), which investigated genetic variants pertaining to loss averse behaviour. The study protocol complied with the Declaration of Helsinki and was approved by the local ethics committee of the Department of Psychology at the University of Bonn.

3.2.2 Electrophysiological recordings

Resting-state EEG was recorded from nine channels (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) with Ag/AgCl electrodes using a BrainProducts System (BrainProducts, Munich, Germany) that consisted of aV-Amp 16 amplifier and VisionRecorder software. AFz was used as a ground electrode. Two additional electrodes were placed on the outer left canthus (HEOG) and below the right eye (VEOG) to record eye movements. During recording the signal was referenced to the left mastoid (M1) and was re-referenced offline to Cz. Data were recorded with a sampling rate of 500 Hz and all electrode impedances were kept below 5 kΩ. During recording a Notch-Filter (50Hz) was applied. We recorded a total of four minutes of resting-state EEG. Participants alternated between eyes-open (20s) and closed (40s) to keep our procedure as close to Gianotti et al. (2009) as possible. However, eyes-open segments were heavily affected by eye motion artifacts, yielding unsatisfactory data. This was also reflected in a very low internal consistency of $\alpha = .5$ between eyes-open and -closed segments. In-keeping with Gianotti et al. (2009) we thus decided to analyze eyes-closed segments only.

3.2.3 Data reduction and analysis

Preprocessing of the EEG data was carried out using BrainVision Analyzer V.1.05 (Brain Products GmbH, Munich, Germany). A 0.5–50Hz band pass filter was applied to the data. Data were then segmented into eyes-open and eyes-closed conditions. The data from the eyes closed conditions were combined (160s) and only recordings from these periods were analysed further (see Gianotti et al., 2009). Data were visually inspected and any obvious muscle artifacts were removed manually. No ocular artifact correction was necessary, given that the data used in the present analysis were obtained only from the eyes closed condition. Additional artifact rejection was carried out based on the criterion of amplitudes exceeding $\pm$200μV. All data were then segmented into 2s epochs with a 50% overlap, in-keeping with previous work considering frontal alpha asymmetry (e.g. Allen, Coan & Nazarian, 2004; Boksem, Smolders & De Cremer, 2012; Hughes et al., 2015). Finally, a fast Fourier transform (FFT) with a 100% Hamming window was used to extract power spectral density (μV^2/Hz). Data were averaged for each EEG channel to produce a single power estimate for each channel. Spectral power in the alpha band (8–12.75Hz) was extracted for each participant from frontal (F3, F4), central (C3, C4) and posterior (P3, P4) sites. Alpha asymmetry in all three locations were considered, given the inconsistent findings from previous studies.

3.2.4 Right frontal asymmetry

Alpha power values from each of the six locations were log transformed to correct for positive skew. Note that we expected to find a link between loss aversion and stronger right- relative to left-hemispheric cortical activation (i.e. greater alpha power in the left- compared to the right-hemisphere). Therefore, we computed asymmetry scores indicating greater left than right alpha power (i.e., stronger right than left cortical activity). This was done for all three recording locations (frontal: F3–F4; central: C3-C4; posterior: P3-P4).

3.2.5 Behavioural testing

Behavioural loss aversion was assessed following the procedure described by Tom et al. (2007) and used previously by our group (Voigt et al., 2015; Markett, Heeren,

Montag, Weber & Reuter, 2016). We presented 256 mixed-gambles that offered a 50% chance to either win or lose a displayed amount of money. Potential gains ranged from 1.00 to 4.00 € with increments of 20 cents and potential losses ranged from 0.50 to 2.00 € with increments of 10 cents. All 256 possible combinations of gains and losses were administered in random order. The range of gains and losses were set to cover the typical range in which loss averse behaviour occurs.

On each trial, participants were asked to either accept or reject the gamble. Participants responded on a 4-point Likert scale ranging from "strongly reject", over "weakly reject", and "weakly accept" to "strongly accept". We used the scale to encourage deliberate answers from the participants. To determine gambling outcome and for our analysis, however, responses were collapsed into a binary "accept" vs. "reject" scheme. A schematic representation of the task is presented in Figure 3.1.

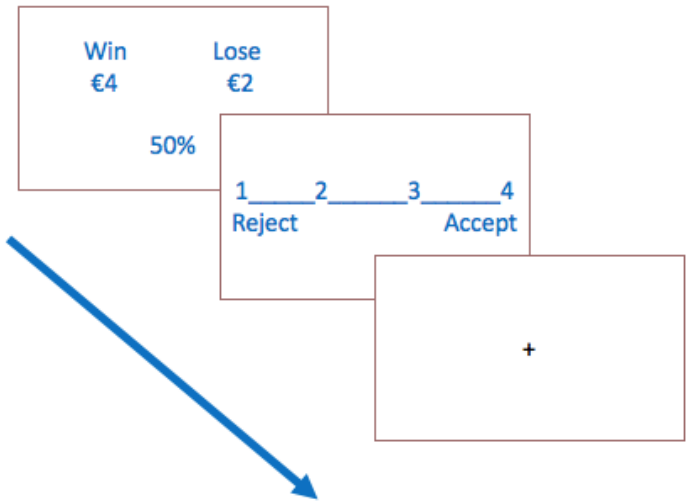

Figure 3.1: A schematic representation of the mixed-gambles task used in the present study

No immediate feedback on gambling outcome was given during the experiment. Prior to the experiment, participants were informed that three of their gambles would be randomly selected and gambled by tossing a coin. Monetary gains and losses arising from these three gambles were either added to or subtracted from an initial endowment of 5.00 € that participants had received prior to the experiment. Thus, participants were aware prior to the experiment that their decision behaviour could lead to actual monetary gain or loss.

The 256 trials were spaced by an 8s inter-trial interval and grouped into five blocks. The inter-trial interval was set to allow for the parallel recording of electrodermal activity (not part of the present report). Between blocks, participants were given the chance to rest for 20 seconds.

The individual loss aversion parameter λ served as main outcome variable. Individual λs were obtained by fitting a separate binary logistic regression model for each participant to predict the binary criterion "accept" vs. "reject" from the gambles' gains and losses. Loss aversion λ was then computed as the ratio of the beta weights for losses and gains ($\lambda = -\beta_{loss} / \beta_{gain}$). This ratio reflects the weighting of gains relative to losses and is commonly used to quantify dispositional loss aversion (Tom et al., 2007; Heeren et al., 2016; Markett et al., 2016).

3.2.6 Psychometric measures

Self-report questionnaire measures assessing avoidance behaviour, specifically the BIS subscale of Carver and White's (1994) BIS/BAS scales and the BIS, Fight, Flight and Freeze subscales of the Jackson-5 (Jackson, 2009) were administered to participants. The BIS (Carver & White, 1994) is a seven-item scale, which assesses participant's likelihood to respond to a perceived threat with anxious or avoidant behaviour. Items are scored on a four-point scale from 1 = *Very True for Me* to 4 = *Very False for me*. The Jackon-5 (Jackson, 2009) was developed to reflect the revised Reinforcement Sensitivity Theory (Gray & McNaughton, 2000) and, as such, distinguishes between BIS as a conflict detection system and the Fight-Flight-Freeze system (FFFS), which controls responses to aversive stimuli. There are three 6-item subscales for FFFS, each scored on a 5-point scale from 1 = *Completely Disagree* to 5 = *Completely Agree*: Fight, which measures the tendency to fight back when faced with a threat; Freezing, which assesses the tendency to physically or mentally stop when faced with a threat; and Flight, which reflects a tendency toward escape when faced with a mildly threatening stimulus (Jackson, 2009). BIS is also a 6-item subscale, scored in the same manner as the FFFS subscales, which assesses anxiety, particularly in situations which entail uncertainty or unknowable social judgements. Additional scales were measured, but

were not examined for the present study as they were not relevant for the hypotheses under test here.

3.2.7 Statistical analyses

To correct for slight positive skew, the loss aversion parameter λ was log transformed. The use of λ or log- λ made no difference to the statistical significance of the results. The main hypotheses were tested using a series of Pearson correlations to assess the strength of relationships between loss aversion (log λ) and alpha power at frontal, central and posterior sites. Post-hoc analysis of the significant relationships between loss aversion and central and posterior right-left asymmetry was carried out to determine the contribution of each hemisphere to the asymmetry scores. This was performed in line with the procedure introduced by Wheeler, Davidson & Tomarken (1993; see also Allen, Coan & Nazarian, 2004). Power at the electrodes where significant relationships were observed (i.e. central site: C3 and C4, and posterior site: P3 and P4) was residualised using a hierarchical regression model with the predictors: 1) average power across all electrode sites, and 2) power from the homologous electrode (i.e. P3 or P4 respectively). Resultant unstandardized residual values from P3 and P4 were then correlated with the loss aversion parameter (log λ). These analyses are included in Appendix B. Rationale for these predictors is discussed in detail by Wheeler, Davidson and Tomarken (1993) and Allen, Coan and Nazarian (2004), but can be briefly summarised as controlling for individual differences, such as scalp thickness and volume conducted activity from the homologous site, with the aim of isolating and retaining power from the approximate region of interest, e.g. the right posterior electrode, P4. Given previous research suggesting gender differences in hemispheric asymmetry (e.g. Baving, Laucht & Schmidt, 2002; Miller, Fox, Cohn, Forbes, Sherrill & Kovacs, 2002; but see also Thibodeau, Jorgensen & Kim, 2006), three moderation analyses were carried out using the PROCESS macro for SPSS (Hayes, 2018) to see whether gender would moderate the relationship between EEG asymmetries and behavioural loss aversion at frontal, central and posterior sites. Correlational analyses of the relationships between behavioural loss aversion and asymmetry indices were conducted with self-reported withdrawal motivation variables: Flight, Fight, Freeze and r-BIS (Jackson, 2009) and BIS (Carver & White, 1994). Finally, three moderation analyses were carried out, using PROCESS (Hayes, 2018),

to examine whether BIS (Carver & White, 1994) would moderate the relationships between cerebral asymmetry and behavioural loss aversion at frontal, central and posterior sites.

3.3. Results

3.3.1 Age and gender effects

Neither age nor gender was associated with the loss aversion parameter log λ (age: r = -.139, p = .393; gender: r = -.086, p = .600). Likewise, asymmetry scores across the three sites were not associated with gender (frontal: r = .025, p = .879; central: r = .174, p = .283; posterior: r = -.053, p = .744) or age (frontal: r = -.143, p = .379; central: r = .059, p = .717; posterior: r = .111, p = .496).

3.3.2 Behavioural data

The mean loss aversion score observed for this sample was 2.02 (SD = 1.11; λ = 2 reflects the aforementioned 2:1 ratio for loss aversion). The median was λ = 1.84. The mean of the log λ values was log λ = .578 (SD = .496).

3.3.3 Relationship between alpha asymmetry and behavioural loss aversion

A series of Pearson's correlations were carried out to assess the relationship between hemispheric asymmetry in the alpha band (scored so that higher values indicate stronger right- than left-hemispheric cortical activity) and behavioural loss aversion as quantified by the log-transformed parameter log λ. The relationship between asymmetry in the alpha band at frontal sites (M = .043, SD = .136) and log λ was non-significant (r = .103, p = .529).

From our exploratory analysis, which did not apply any corrections for multiple comparisons, a significant relationship was observed between alpha asymmetry at central recording sites (M = .244, SD = .235) and log λ (r = .348, p = .028, 95% CI [.040, .655]). Similarly, a significant relationship was found between cortical asymmetry scores at posterior sites (M = .119, SD = .322) and log λ (r = .482, p = .002,

95% CI [.195, .770]). After correction for multiple comparisons ($\alpha = 0.05 / 3 = 0.017$), only the relationship between log λ and posterior right cortical asymmetry remained significant. The relationships between log λ and frontal and posterior asymmetries are depicted in Figures 3.2 and 3.3 below.

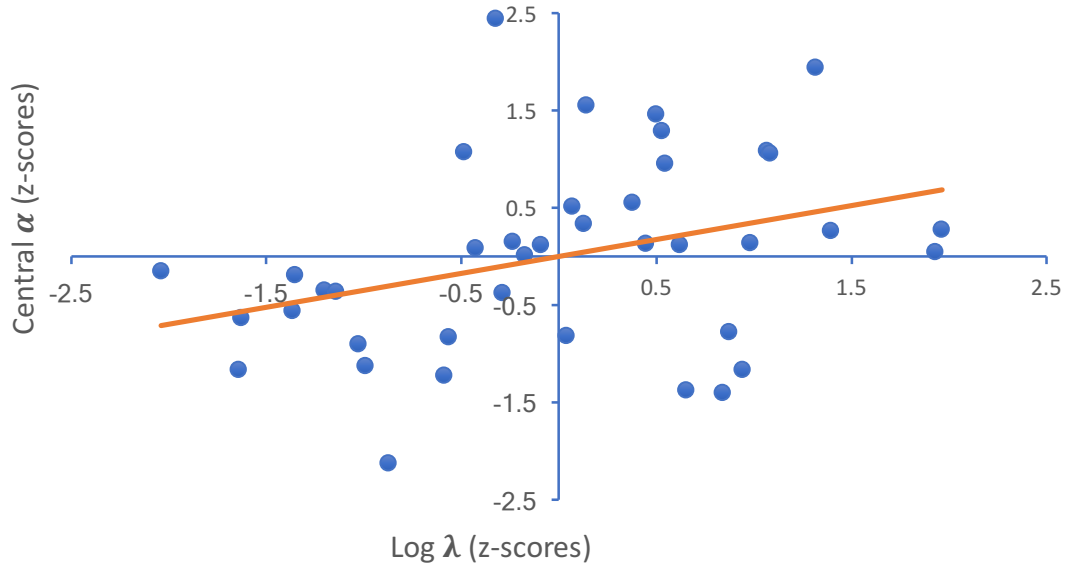

Figure 3.2: Correlational relationship between right-left asymmetry at central electrodes and log-transformed loss aversion parameter λ.

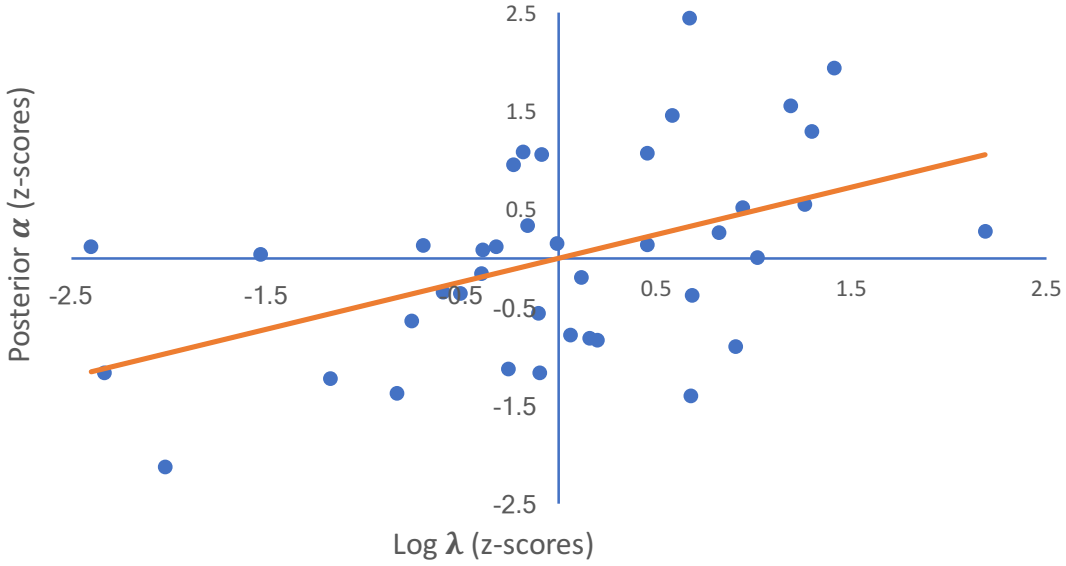

Figure 3.3: Correlational relationship between right-left asymmetry at posterior electrodes and log-transformed loss aversion parameter λ.

Supplementary Analyses

3.3.4 Respective right and left hemisphere contributions to alpha asymmetry

To parse the relative contributions of the right and left hemispheres to the asymmetry scores at central and posterior locations, a hierarchical regression model was created with two predictors: 1) Average power across all scalp-recorded electrodes, and 2) power from the homologous electrode site (e.g. for the left-side electrode C3, its right-sided homologue is C4). The electrode of interest (i.e. C3 / C4 / P3 / P4) was set as the dependent variable for each model. Resultant unstandardized residual values for C3, C4, P3 and P4 (i.e. the dependent variables) were then correlated with the loss aversion. The results of these correlations are presented in table 3.1. For both central and posterior sites, a similar pattern of cortical activation can be observed as influencing the asymmetry score. Specifically, increased activation in the right hemisphere (i.e. decreased α power, as indicated by the negative sign) and decreased activation in the left hemisphere (i.e. increased α power, as indicated by the positive sign) are both significantly related to the loss aversion parameter log λ.

Table 3.1: Correlations between loss aversion (log λ) and the unstandardized residual α power indices at central and posterior left and right hemisphere electrodes

	Right Hemisphere		Left Hemisphere	
	C4	P4	C3	P3
log λ				
r	-.349	-.376	.333	.478
p	.028	.017	.036	.002*
95% CI	[-.656, -.041]	[.024, .643]	[.189, .766]	[-.680, .072]

*Significant at α corrected for multiple comparisons (0.05 / 6) = 0.008.

3.3.5 Gender as a moderator of the relationship between EEG alpha asymmetry and loss aversion

Given the occasionally observed gender differences in the literature on alpha asymmetry (e.g. Smit, Posthuma, Boomsma & De Geus, 2007, but see also Thibodeau, Jorgensen & Kim, 2006), three moderation analyses were run to investigate whether

gender would moderate the relationship between loss aversion and alpha asymmetry at frontal, central and posterior sites. Each moderation was run using the PROCESS macro for SPSS (Hayes, 2018). Thus, loss aversion was set as the dependent variable and alpha asymmetry and gender were entered as predictors. The interaction term between gender and alpha asymmetry was the moderator for each respective location, i.e. frontal, central and posterior. No significant moderating effect of gender was observed on the relationship between loss aversion and alpha asymmetry at frontal electrodes. The overall model was non-significant (R^2 = .25, F (3, 36) = .7677, p =.5197), with no significant predictors observed for frontal asymmetry (b = .988, t (36) = 1.30, p = .20); gender (b = .045, t (36) = .559, p = .58); or the interaction (b = .884, t (36) = 1.30, p = .21).

Similarly, the overall model effect for central electrodes was non-significant (R^2 = .39, F (3, 36) = 2.196, p =.105). Central asymmetry was a significant predictor of loss aversion (b = .759, t (36) = 2.29, p = .028), however, this relationship does not survive correction for multiple comparisons (α = 0.05/ 3 = 0.017). Neither gender (b = .07, t (36) = .91, p = .37), nor the interaction term between gender and alpha asymmetry (b = .243, t (36) = .71, p = .48) were significant. Thus, no moderating effect of gender was observed for the relationship between asymmetry at central electrodes and loss aversion.

Finally, no effect of gender as a moderator was observed on the relationship between alpha power at posterior electrodes and loss aversion. The overall model was significant (R^2 = .49, F (3, 36) = 3.87, p =.017) and alpha power at posterior sites was a significant predictor of loss aversion (b = .713, t (36) = 3.13, p = .003). No significance was observed for the predictor gender (b = .029, t (36) = .409, p = .685) or for the interaction term (b = -.134, t (36) = -.598 p = .554). Thus, there was no evidence to suggest a moderating effect of gender on the relationship between alpha asymmetry and loss aversion at frontal, central or posterior sites. It should also be noted that this analysis was underpowered and that these results should be interpreted with caution.

3.3.6 Alpha asymmetry, loss aversion and psychometric measures of withdrawal motivation.

Means and standard deviations for the other self-report variables are presented in table 3.2. Correlational analyses examined the relationships between loss averse behaviour (logλ), increased right (relative to left) asymmetry and the BIS (Carver & White, 1994), r-BIS, Flight, Fight and Freeze scales of the Jackson-5 (Jackson, 2009). These analyses involving asymmetry were restricted to central and posterior sites, as these were the sites where there were (near-) significant relationships between loss aversion and asymmetry were observed. These correlations were also exploratory and uncorrected for multiple comparisons. As a result, they should be treated with caution.

Table 3.2: Means and standard deviations for self-report variables

	Mean	SD
BIS	20.71	4.35
rRST BIS	2.64	.42
Flight	2.45	.47
Fight	2.53	.49
Freeze	2.65	.37

Weak relationships were observed between these self-reported measures of avoidance and behavioural loss aversion. The strongest relationship was observed between Flight and central alpha asymmetry. Specifically, increased right asymmetry was associated with Flight at central, but not posterior sites (central α r = .366, p = .036, 95% CI [.025, .70]; posterior α r = -.025 p = .889). However, this relationship does not survive correction for multiple comparisons (α = 0.05 / 15 = .003). No other convincing relationships were observed between the psychometric variables and the asymmetry indices. Information for all correlations is presented in table 3.3.

Table 3.3: Correlations between loss aversion (log λ) and α asymmetry indices at central and posterior sites with psychometric measures of avoidance.

	log λ	Central α	Posterior α
BIS			
r	.135	.278	.139
p	.454	.118	.439
rRST BIS			
r	-.142	-.224	-.039
p	.424	.202	.202
Flight	-.216	.366*	-.025
r	.228	.036	.889
p			
Freeze			
r	.297	.158	.158
p	.093	.380	.380
Fight			
r	.138	.204	.207
p	.444	.256	.247

*p < 0.05 (not adjusted for multiple comparisons 0.05/ 15 = 0.003).

3.3.7 BIS as a moderator of the relationship between cortical asymmetry and loss aversion

Given the lack of a clear relationship between BIS and loss aversion or cerebral asymmetry and, in light of work by Studer, Pedroni and Rieskamp (2013) reporting a modulating effect of BIS on the relationship between risk taking and EEG asymmetry in the theta band, three moderation analyses were carried out to see if BIS would moderate the relationship between alpha asymmetry and behavioural loss aversion at frontal, central and posterior sites. Each moderation was run using the PROCESS macro for SPSS (Hayes, 2018). Thus, loss aversion was set as the dependent variable and alpha asymmetry and BIS were entered as predictors. The interaction term between BIS and alpha asymmetry was the moderator for each respective location, i.e. frontal, central and posterior.

Model 1 tested whether BIS would moderate the relationship between alpha asymmetry at frontal electrodes and behavioural loss aversion. The overall model was non-significant (R^2 = .14, F (3, 30) = .1.66, p =.197). No significant main effect was observed for frontal alpha asymmetry (b = -.335, t (30) = 6.64, p = .73) or for BIS (b =

.0173, t (30) = .827, p = .42). The interaction term approached significance, but this result would not withstand correction for multiple comparison (α = 0.05/ 3 = 0.017) (b = -.492, t (30) = -1.96, p = .0598), suggesting no significant moderating effect of BIS on the relationship between frontal alpha asymmetry and behavioural loss aversion

Model 2 tested whether BIS would moderate the relationship between alpha asymmetry at central electrodes and behavioural loss aversion. The overall model was non-significant (R^2 = .15, F (3, 30) = .1.76, p =.176). No significant main effect was observed for central alpha asymmetry (b = .74, t (30) = 1.73, p = .094) or for BIS (b = .005, t (30) = .206, p = .84). The interaction term was also non-significant (b = -.073, t (30) = -.713, p = .481), suggesting no significant moderating effect of BIS on the relationship between central alpha asymmetry and behavioural loss aversion

Model 3 tested whether BIS would moderate the relationship between alpha asymmetry at posterior electrodes and behavioural loss aversion. The overall model was significant (R^2 = .351, F (3, 30) = 5.41, p = .0043). This relationship survived correction for multiple comparisons (α = 0.05/ 3 = 0.017). The overall model significance was driven by a significant main effect, observed for posterior alpha asymmetry in predicting behavioural loss aversion (b = .818, t (30) = 2.87, p = .008). This reflects the correlational relationship reported in section 3.3.3, i.e. that relatively greater right (than left) posterior asymmetry was associated with greater behavioural loss aversion. In contrast, no significant main effect was observed for BIS (b = .012, t (30) = .626, p = .54). The interaction term was also non-significant (b = .102, t (30) = 1.23, p = .21), suggesting no significant moderating effect of BIS on the relationship between posterior alpha asymmetry and behavioural loss aversion.

3.4. Discussion

We recorded resting state EEG activity from participants before they engaged in a mixed gambles task, designed to assess behavioural loss aversion. Behavioural loss aversion was associated with cortical asymmetry, as expected: stronger right- than left-hemispheric activation (i.e. lower right relative to left alpha power) was associated with higher levels of loss aversion. Interestingly, this effect was observed only for posterior

electrodes (P3–P4). We predicted that this effect would be observed at frontal sites, rather than at those sites investigated in the exploratory analysis (i.e. central and posterior). Thus, in the present study, participants with greater right (relative to left) tonic cortical activity in central and posterior regions showed greater behavioural loss aversion when undertaking gambles with a 50% chance of winning or losing money.

Our mean loss aversion index (Lambda, λ) of 2.02 reflects previous findings (e.g., Haigh & List, 2005; Heeren et al., 2016; Johnson & Goldstein, 2003, Post et al., 2008; Tovar, 2009) and is in keeping with the observation of Kahneman (2003) that, as individuals tend to be loss averse, they will accept 50/50 gambles, on average, only when the amount they stand to win exceeds that they stand to lose at a ratio of 2:1. The finding that loss averse behaviour is associated with greater right cortical activity is also in keeping with previous findings from patients with brain damage to the right hemisphere, who demonstrate decreased loss aversion in the form of more risky decisions on gambling tasks (e.g., Rahman et al., 2001; Clark et al., 2003; Tranel, Bechara & Denburg, 2002). This literature implicates the lateralisation of the right hemisphere in economic decision making (see Gianotti et al., 2009; Knoch, Gianotti, Baumgartner, & Fehr, 2010; Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006) and that individual differences in the neural function of the right hemisphere may lead to variation in behavioural loss aversion.

While our findings are in keeping with the notion that lateralisation of the right hemisphere may underlie individual variation in behavioural loss aversion, the research attempting to characterise the neural bases of this variation is less convincing. EEG studies have attempted to broadly localise asymmetries in participants' resting state EEG recordings to frontal, central, or posterior sites. Resting state EEG asymmetry has been found to be a relatively stable marker of behavioural approach and avoidance over a period of months to years (e.g., Brooker, Canen, Davidson & Goldsmith, 2017; Davidson, 2004; Jones, Field, Davalos & Pickens, 1997; Tomarken et al., 1992; Vuga, Fox, Cohn, Georger, Levenstein & Kovacs, 2006, though see also Wacker, Chavanon & Stemmler for a meta-analysis suggesting that this link is less robust than is typically assumed). EEG research on behavioural loss aversion, a putative avoidance behaviour, is scarce and reports mixed findings both in terms of the oscillations studied and the locations in which the asymmetries are observed. Previous studies indicate a

relationship between behavioural approach and increased left relative to right activity, as assessed via alpha-band oscillations in the PFC (e.g., Hughes et al., 2015; Pizzagalli et al., 2005). Moreover, TMS research by Knoch et al. (2006a) suggests a causal role for the right dorsolateral PFC in moderating risky decisions. A large body of developmental literature also associates avoidance behaviours with right (relative to left) frontal asymmetry in children (see Gander & Bucheim, 2015 for a review). Based upon these findings, we expected to observe a link between loss aversion and frontal alpha-band asymmetry. Somewhat surprisingly, we observed a robust association only at posterior recording sites, which could not be observed at frontal locations. This finding, though unpredicted, supports earlier work by Schutter and van Honk (2005), who found that the relative proportion of low-frequency oscillations at parietal sites was significantly associated with risky decision making.

This pattern of EEG asymmetry may also mirror the interaction of functional networks, identified in fMRI paradigms and thought to characterise psychiatric disorders. For example, Sylvester et al. (2012) have proposed that increased functioning of the cingulo-opercular and ventral attention networks in concert with decreased functioning of the default mode and fronto-parietal networks may be associated with anxiety. Focusing on research utilising non-emotionally valenced tasks, such as the Tom et al. (2007) task used in the current study, they outline a framework in which high-anxiety individuals show decreased connectivity between areas in the cingular-opercular network, specifically the dorsal anterior cingulate cortex (dACC), and the frontoparietal network, in particular the dorsolateral prefrontal cortex. Uniquely among these networks, the frontoparietal network is thought to be lateralised so that the left and right hemispheres mirror one another's functioning (Smith et al., 2009). Given findings by Gorka, Phan & Shankman (2015) on the convergence of EEG asymmetry and fMRI measures during reward anticipation, it seems plausible that EEG indices may reflect the functioning of such networks, however, additional research is required to test this hypothesis.

Viewing loss aversion as a type of anxiety is arguably better grounded in the revised Reinforcement Sensitivity Theory (r-RST; Gray & McNaughton, 2000), in which BIS is proposed, not as an avoidance system, but as a conflict-monitoring system, which may be related to trait anxiety. Given cross-species observations of how unpredictable

or uncertain outcomes provoke anxiety (e.g., Grillon, Baas, Lissek, Smith & Milstein, 2004), it seems reasonable to view loss aversion as reflective of an anxious response to an uncertain gamble, in which an individual can gain or lose money. Indeed, previous research has linked anxiety and risk aversion in a social context (Lorian & Grisham, 2010). Given that risk aversion is thought to arise as a result of loss aversion (Kobberling & Wakker, 2005), it seems reasonable to think that our results may reflect an element of anxiety. In keeping with this idea, Sokol-Hessener et al (2009) found a relationship between loss aversion and physiological arousal in response to loss as measured by skin conductance response (SCR). Interestingly, it has been suggested that stronger right- than left-hemispheric activity in posterior regions is a neocortical substrate of anxiety (Bruder et al., 1997; Heller, Etienne & Miller, 1995; Kentgen, Tenke, Pine, Fong, Klein & Bruder, 2000). Therefore, the link between behavioural loss aversion and posterior cortical asymmetry reported in the present study may indirectly support the notion that loss aversion involves (or derives from) anxiety. To our knowledge, no task has explicitly assessed loss aversion, anxiety and EEG asymmetries, so further research is needed in order to substantiate this interpretation.

Despite the plethora of studies that have investigated EEG asymmetry indices in the past four decades, few have sought to consider the relative contribution of activity in each hemisphere to the asymmetry index. Instead, such studies typically relate the relationship between the asymmetry difference score to a psychometric or behavioural variable. This asymmetry score conflates the contribution of both hemispheres to the asymmetry score, which obscures the relationship of each individual hemisphere to the variable of interest. Consideration of the individual contribution of each hemisphere is arguably more in keeping with the original model of lateralised approach / withdrawal (Davidson, 1992), given its basis in observations of unilateral brain injuries and subsequent depressive / manic behaviours. Thus, it can be argued that the respective relationship of each hemisphere to the variable of interest should be investigated and the asymmetry score alone is uninformative. Given this discrepancy in the literature, post-hoc analyses were run in the present study to parse the relative contributions of left and right alpha asymmetry. These analyses indicated that the asymmetry scores at central and posterior electrodes (i.e. those significantly related to loss aversion) were driven by a combination of increased right cortical activation (i.e. lower right – relative to left – alpha power) and diminished left cortical activation (i.e. greater right – relative

to left – alpha power). Only one of these relationships survived correction for multiple comparisons: the relatively greater contribution of left posterior alpha asymmetry (indicative of decreased left cortical activity) at posterior electrodes. Despite the absence of significant results in these analyses, the overall correlation pattern is indicative of negative relationships for right hemisphere alpha asymmetry (suggesting greater right-sided cortical activity) and positive relationships for left hemisphere alpha activity (indicative of decreased left-sided cortical activity) for both central and posterior sites. Viewed in terms of Davidson's (1992) theory, this suggests that the cerebral asymmetry scores reflect a combination of greater avoidance motivation (reflected in the relatively higher right cortical activation) and decreased approach motivation (reflected in the relatively lower left cortical activation). To our knowledge, the relative contributions of each individual hemisphere to an asymmetry score associated with loss aversion have not previously been calculated.

This method of parsing the relative contribution of each hemisphere to the asymmetry score was first proposed by Wheeler, Davidson and Tomarken (1993). For a general self-report measure of negative emotional reactivity (fear and disgust), they identified a different pattern to that observed in the present study: only greater right activation (i.e. decreased alpha power) was significantly linked to the experience of negative affect. In contrast, Harmon-Jones and Allen (1997) noted that both hemispheres contributed to an asymmetry index linked to anger, such that greater right alpha (i.e. relatively less right than left activation) was positively related to the experience of anger, whereas decreased left alpha (i.e. relatively greater left than right activation) was negatively correlated with the experience of anger. It should be noted, that this method has received some criticism (see, for example, Allen, Coan & Nazarian, 2004) and some alternative methods of parsing the relative contributions of each hemisphere to the asymmetry index have been proposed (e.g. Coan & Allen, 2003). This need to parse the relative contributions has been underemphasised in the literature, e.g. a recent primer on frontal asymmetry neglected any mention of individual hemispheric contributions to the asymmetry score (Smith, Reznik, Stewart & Allen, 2017).

A related, but small, body of work has attempted to isolate the sources of EEG alpha asymmetry and these studies implicate frontal regions of both the left and right hemispheres. Work by the Pizzagalli lab used current source density modelling to relate

decreased alpha activity (indicating greater cortical activation) in the left dorsolateral prefrontal cortex, medial orbitofrontal cortex and left parietal with a stronger reward bias on a signal detection task (Pizzagalli, Sherwood, Henriques & Davidson, 2005). Participants with greater activity in these areas were more likely to define an ambiguous stimulus as a target when a reward was involved, compared to participants with less activity in these regions, thus, suggesting a relationship between greater left cortical activation and higher approach motivation. These findings are tentative, based on a sample of just eighteen participants. However, subsequent, better-powered work, seems to echo the left-lateralised source for approach motivation. Koslov, Mendes, Pajtas & Pizzagalli (2011) implicated relatively greater left cortical activation (reflected in relatively decreased EEG alpha activity), source localised to Brodmann's Area 9 in the left dorsolateral prefrontal cortex (DLPFC), in an approach state in response to threatening social evaluation. Complementary findings emerge from the work of Shackman, Menamin, Maxwell, Greischar and Davison (2009), who reported that increased right, relative to left, cortical activity, localised to the right DLPFC (Brodmann's Area 9), was related to higher scores on BIS scale (Carver & White, 1994).

The above studies, though limited in number (and, in some cases, with low statistical power), lend some tentative support to the idea that approach and withdrawal tendencies are lateralised. It is also possible that different structures in the frontal cortex can result in the same downstream phenomena, e.g. self-reported affect. Thus, while greater sensitivity to reward has been linked with increased activation in the left (relative to the right) hemisphere (Pizzagalli et al., 2005) and greater BIS sensitivity has been linked to increased right (relative to left) hemispheric activity (Shackman et al., 2009), a deficit in either system could facilitate the development of a depressive phenotype (Smith et al., 2017). Alternatively, discrete patterns of left and right hemispheric asymmetry, which are opaque when considered as a relative ratio, may characterise different traits / psychopathologies (e.g. the different patterns of hemispheric activity related to anger (Harmon-Jones & Allen, 1998), disgust and fear (Wheeler, Davidson & Tomarken, 1993 - discussed above). Additional work is needed to classify the neural structures underlying frontal asymmetry and to clarify their relationship to behavioural phenotypes, however, isolating the relative contributions of each hemisphere to the asymmetry score is an important first step in this respect.

Contrary to the occasionally observed gender differences in the literature (e.g. Smit, Posthuma, Boomsma & De Geus, 2007), supplementary analyses for the current study, although underpowered, did not suggest a different pattern of relationship between hemispheric asymmetry and loss aversion for females compared to males. Sex-specific patterns of neural asymmetry have been reported in the literature considering individual differences in hemispheric asymmetries. Baving, Laucht & Schmidt (2002) report greater right than left frontal activation in a group of 8 to 11-year-old girls with anxiety compared to their male peers, who showed greater left than right activity. Miller et al. (2002) identified the same patterns in female and male adults with a history of childhood depression. These gender differences are not always clear-cut, however, and Kline, Allen & Schwartz (1998) report contrary results. Furthermore, in a meta-analysis, Thibodeau, Jorgensen & Kim (2006) investigated gender as a moderator of frontal alpha EEG asymmetry and found no influence of gender on effect size. Taken together, these findings suggest that any potential moderating effects of gender on cerebral asymmetry are more nuanced than commonly thought and require more precise characterisation.

The hypotheses for the present study were based on the conception of loss aversion as a type of avoidance behaviour, reflecting Gray's (1972) BIS system. Contrary to earlier work, e.g. Studer, Pedroni & Rieskamp (2013), we did not observe a relationship between BIS, as measured by Carver and White's (1994) BIS / BAS scale and behavioural loss aversion. This is not surprising, given suggestions that the relationship between avoidance behaviours and the BIS may be more complex than that often observed between BAS and frontal asymmetry (Coan & Allen, 2004, 2003, Harmon-Jones & Allen, 1997). The expected relationships are complicated by the reconceptualization of BIS in the rRST (Gray & McNaughton, 2000). The rRST conceptualises BIS as a system responsible for regulating goal conflict. In contrast, the original theory viewed BIS as the mechanism underlying withdrawal motivation. Much of the literature considering the relationship between EEG asymmetry and behavioural withdrawal continues to rely on the oRST (see Gable, Neal & Threadgill, 2018 for a discussion). This reliance on out-dated theory may help to account for mixed findings in attempts to link cerebral asymmetries to withdrawal motivation. In their discussion of this issue, Gable, Neal and Threadgill (2018) argue that the revised BIS, i.e. a goal-

conflict regulatory system, may be better linked to cortical asymmetries than the oBIS (i.e. a relatively straight forward withdrawal motivation system). Specifically, they argue that greater activation of rBIS would be associated with greater right frontal asymmetry, whereas reduced rBIS would be linked to relatively decreased right frontal asymmetry (i.e. relatively greater left frontal asymmetry). It remains unclear, however, whether this relationship between rBIS and frontal asymmetry is characterised by inhibition of the left frontal cortex or greater activation of the right frontal cortex, further underscoring the need to conduct analyses to parse the relative contributions of the two hemispheres to the EEG asymmetry score.

This discussion is interesting in light of previous work reporting a relationship between BIS and EEG indices of withdrawal motivation (e.g. Studer, Pedroni & Rieskamp, 2013; Massar, Rossi, Schutter & Kenemans, 2012). Studer, Pedroni and Rieskamp (2013) argue that their data demonstrated a modulatory role for BIS on the relationship between risk taking and frontal EEG asymmetry in the theta band. Specifically, they report a significant interaction between BIS scores and right (relative to left) frontal asymmetry in the theta band in predicting risk taking behaviour. This finding suggested a moderating effect of BIS, whereby greater right frontal asymmetry in the theta band was a stronger predictor of risk taking behaviour in participants with high BIS scores (Carver & White, 1994), relative to individuals with low BIS scores. Given this observation, our supplementary analyses sought to examine whether BIS would moderate the relationship between cerebral asymmetry, assessed in the alpha band, and behavioural loss aversion. Contrary to the findings of Studer, Pedroni and Rieskamp (2013), BIS did not moderate the relationship between alpha asymmetry and behavioural loss aversion at frontal, central or posterior sites. Caution is advised in interpreting these findings, given the relative small sample size in the present study. N = 34 for the moderation analyses using BIS (due to missing questionnaire data), indicating that these analyses were underpowered. In contrast, the study by Studer, Pedroni and Rieskamp included 70 participants. Thus, the results of these moderation analyses need to be replicated in a larger sample.

The present study also sought to characterise the relationships between cerebral asymmetries, behavioural loss aversion and self-report measures of withdrawal motivation and BIS. The largest correlation observed in the present study was between

central alpha asymmetry and the flight subscale of the Jackson-5 (Jackson, 2009), though this did not achieve significance after correction for multiple comparisons. To our knowledge, this is the first study to demonstrate a neural relationship with a subscale of the Jackson-5 (see Walker & Jackson, 2017). The flight subscale assesses the tendency toward escape when faced with a mild threat. With respect to the present loss aversion task, it could be suggested that by choosing to reject the 50 / 50 gamble, participants are attempting to 'escape' the threat of losing money. This is a highly speculative suggestion and further research would be needed to substantiate this idea. Beyond this, the absence of any substantial correlations between self-report measures of withdrawal motivation and behavioural loss aversion or right cerebral asymmetries is surprising. Previous work (e.g. Studer, Pedroni & Rieskamp, 2013) report a relationship between BIS scores (Carver & White, 1994) and financial risk taking, whereby individuals with higher BIS scores were less likely to make risky decisions on a gambling task. Similarly, prior work by Gianotti et al (2009) identified a role for right (relative to left) cortical activity in individual risk taking behaviour. Specifically, they found that healthy participants with higher resting state activity in the right (compared to the left) PFC showed lower levels of risk averse behaviour on a risk-taking task (the devil's chest).

A putative explanation for these discrepant findings may reside in the fact that both these studies used gambling tasks that assessed risk aversion, rather than loss aversion per se. Although risk aversion is thought to arise as a result of loss aversion (Kobberling & Wakker, 2005), the two constructs are somewhat dissociable. Kahneman and Tversky (1979) point out that risk aversion is the preference for any certain prospect over any risky prospect with the same value. Thus, when faced with any form of uncertainty, people who are risk averse seek to minimise the uncertainty. Loss aversion refers to an explanatory model put forward by Kahneman and Tversky (1979) to explain how risk aversion may arise. Briefly, loss aversion dictates that putative losses are more salient to people than are putative gains. Thus, loss aversion is reliant on some form of relative cost / benefit trade off, compared to the goal of minimising uncertainty. The tasks used by Gianotti et al. (2009) and Studer, Pedroni and Rieskamp (2013) both assess risk aversion. That is, they both offer the participant the choice between a small, certain reward or the option to take a risk to obtain a larger, uncertain reward. In contrast, no certain 'win' was offered by the gambling task in the present study.

Participants were presented with a series of gambles that offered a 50% chance to either win or lose a displayed amount of money (potential gains ranged from €1.00 to 4.00 with increments of 20 cents, and potential losses ranged from 0.50 to €2.00 with increments of 10 cents). For each trial, participants were asked to either accept or reject the gamble, rather than having a certain alternative. Thus, the task used in the present study assessed the relative salience of losses and gains for the participants (loss aversion) and this distinction may partially explain our inability to replicate the findings from Gianotti et al. (2009) and Studer, Pedroni and Rieskamp (2013).

Finally, it should also be acknowledged that the research on frontal asymmetries and behavioural approach and withdrawal is not always clear-cut. Several methodological issues have been identified in research in this area, including a lack of attention paid to whether different regions (frontal, central, posterior) are differentially involved in specific tasks or act as a function of individual differences (see Allen, Coan & Nazarian, 2004 and Hagemann, 2004 for a discussion). Additionally, a meta-analysis by Wacker, Chavanon & Stemmler (2010) suggests that the relationship between frontal asymmetries and indices of behavioural approach are much weaker and more inconsistent than is typically assumed. In addition to this problem, studies considering frontal asymmetries have not always reported the corresponding asymmetry values for central and posterior locations (Jesulola, Sharpley, Bitsika, Agnew & Wilson, 2015), making it difficult to confirm the specificity of these findings.

Several limitations from this study must also be acknowledged. Firstly, many of the confidence intervals associated with the significant results in the present study are quite wide. Thus, we urge caution in extrapolating from these results and emphasise the need for future work to replicate these findings. Secondly, EEG data were obtained from only nine electrodes. While these electrodes represent the most frequently investigated sites in EEG asymmetry research, it does limit our ability to test the specificity of our findings to these locations. Thirdly, we collected a relatively small amount of resting state data: just 160s from four intervals in which participants alternated between keeping their eyes open and closed. Experimental procedures in this area typically report a recording of 8 minutes, in which participants alternate between keeping their eyes open or closed. However, good reliability (Cronbach's alpha of 0.80 – 0.90) has been reported for recordings of 4 minutes duration (Hagemann, Naumann, Becker,

Maier & Bartussek, 1998). Finally, it should be noted that we only report frequencies extracted from the alpha band in the current study, as our hypotheses were restricted to this frequency band. Given findings associating avoidance behaviours with cortical asymmetry in other frequency bands (e.g., theta, delta, beta), additional research is required to investigate the specificity of each frequency band to individual differences in loss aversion specifically and approach/avoidance behaviours more generally.

3.5. Conclusion

These results indicate that stronger right, relative to left, tonic activity (i.e. greater left relative to right alpha power) in central and in posterior cortical regions is associated with loss averse behaviour. Supplementary analyses indicate that this relationship is driven by a combination of increased right and decreased left hemispheric activation and that the relationship between hemispheric site and loss aversion appears unaffected by gender difference or relative levels of trait BIS. Supplementary analyses yielded no significant relationships between EEG indices of right asymmetry and traditionally and widely-used psychometric measures, which putatively reflect individual differences in withdrawal system reactivity. The numerically largest relationship observed in these analyses was between EEG asymmetry and a less-commonly used measure of withdrawal sensitivity: The Flight subscale of the Jackson-5. This represents the first work suggesting a link between a sub-scale of the Jackson-5 and a putative neural index of reward processing. These results contribute to the crucial, but currently limited existent literature investigating the neural basis of loss aversion and the characterisation of withdrawal motivation and BIS.

Chapter 4

Development and confirmatory analysis of the Goldsmiths Anhedonia Measure (GAME)

Overview

As recognition of the multifaceted nature of anhedonia has grown, self-report measures have evolved to reflect different domains of reward processing. Despite the emergence of a plethora of questionnaires designed to assess anhedonia in recent years, there remain discrepancies in the number and nature of factors captured by these measures. This study sought to develop a new measure of trait anhedonia, designed to assess individual differences in the healthy population. Existent questionnaires prior to 2015 (i.e. when data collection for the present study began) were examined to produce a list of 171 unique items tapping different aspects of reward processing. The items were re-worded and placed on a five-point Likert scale. 51-items were selected to form a new self-report measure of anhedonia, based on an Exploratory Factor Analysis in a community sample of 523 participants. Based on these data, a four-factor structure was deemed the most parsimonious account of the 51 items. The four factors reflected Social, Emotional, Aesthetic and Novelty-Seeking (Drive) aspects of hedonic experience. A subsequent study was conducted to confirm the factor structure of this questionnaire. A new sample of 311 participants completed the 51-item measure, as well as other measures of reward processing and personality to assess the validity of the Goldsmiths Anhedonia Measure (GAME). A Confirmatory Factor Analysis was performed on the data. Fit indices, RMSEA, SRMR and CFI suggested adequate fit. The psychometric properties of this new measure are discussed, including the implications of conflicting fit indices and the relationship of this putative new measure to existing anhedonia questionnaires and other aspects of personality. The need for a valid instrument, sensitive to individual differences in anhedonia, that accurately reflects the theoretical understanding of the concept is emphasised in this chapter.

4.1 Introduction

4.1.1 Conceptualisation of anhedonia

Deficits in reward processing are observed across a host of psychiatric and neurological disorders, including depression (Pelizza & Ferrari, 2009; Yuen et al., 2015), schizophrenia (Strauss, Waltz & Gold, 2014), Parkinson's Disease (den Brok, van Dalen, van Gool, Moll van Charante, de Bie & Richard, 2015), and addiction (Markou, Kosten & Koob, 1998). Such deficits can also be conceptualised on a reward processing continuum, e.g. anhedonia. Individual differences in these dispositions can be observed in a trait-like manner across non-clinical, as well as clinical populations (e.g. Blanchard, Horan & Brown, 2001; Franken, Rassin & Muris, 2007; Harvey, Pruessnet, Czechowska & Lepage, 2007; Herbener, Harrow & Hill, 2005; Treadway, Buckholtz, Schwartzman, Lambert & Zald, 2009).

Individual differences in trait anhedonia, thought to reflect a lack of sensitivity or motivation toward pleasure (APA, 2013), have been proposed as a putative marker for the development of depression and schizophrenia (Hasler, Drevets, Manji & Charney, 2004; Pizzagalli, 2014). Anhedonia also demonstrates efficacy as a predictor of treatment outcome in depression (McMakin et al., 2012; Uher et al., 2008). As interest in the predictive utility of anhedonia has grown, so too has interest in accurately assessing and measuring relative levels of anhedonia in the general population to enhance understanding of its foundation and development. A plethora of methods exist that attempt to assess anhedonia, spanning neuroimaging, behavioural and self-report methods. Self-report methods are a particularly convenient, practical and cheap measurement tool, for both healthy and clinical samples. Reflecting this utility, a host of self-report questionnaire measures of anhedonia have been developed in recent years (see table 4.1).

Table 4.1 Questionnaire measures assessing anhedonia and their factors

Scale	**Authors**	**Description**	**Factors**	**Reliability** (Cronbach's α)	**Population tested**
Chapman Physical and Social Anhedonia scales	Chapman et al. (1976) Revised by Eckbald et al. (1982)	True / False scale 61 items (physical) 40 items (social)	2: social anhedonia; physical anhedonia	Males: α = .74 (Physical) α = .85 (Social) Females: α = .66 (Physical) α = .82 (Social)	Patients (schizophrenia) and controls
Fawcett-Clark Pleasure Scale (FCPS)	Fawcett et al. (1983)	36-item 9-point scale	1: consummatory pleasure	α = .85	Patients (depression)* and controls
Snaith Hamilton Pleasure Scale (SHAPS)	Snaith et al. (1995)	14-item 4 options: strongly disagree – strongly agree	1: consummatory pleasure	α = .86 (patients)ǂ	Patients (depression)* and controls
Temporal Experience of Pleasure Scale (TEPS)	Gard et al. (2006)	18-item 6-point scale	2: anticipatory pleasure (A); consummatory pleasure (C)	α = .72 (Ant) α = .64 (Con) α = .78 (combined)	Healthy controls
Motivation and Pleasure Scale (MAP-SR)	Llerena et al. (2013)	15-item 5-point scale	3: work / recreation; interpersonal	α = .90	Patients (schizophrenia)*

			relationships; activities/ hobbies		
Specific Loss of Interest and Pleasure Scale (SLIPS)	Winer et al. (2014)	23-item 4 options assessing level of change in social anhedonia	1: social anhedonia (recent changes)	α = .94	Healthy controls
Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS)	Gooding & Pflum (2014)	17-item 6-point scale	3: intimate social interactions; group social interactions; social bonding	α = .86	Healthy controls
Dimensional Anhedonia Rating Scale (DARS)	Rizvi et al. (2015)	17-item 5-point scale	4: hobbies; food/ drink; social activities; sensory experiences	α = .91 (hobbies) α = .86 (food/drink) α = .83 (social) α = .89 (sensory) α = .92 (combined)	Patients (depression) and controls
Apathy Motivation Index (AMI)	Ang et al. (2017)	18-item 5-point scale	3: behavioural; social; emotional	α = .79 (behavioural) α = .75 (social) α = .75 (emotional) α = .77 (combined)	Healthy controls

*describes main diagnosis of patient group; multiple diagnostic groups included

+only data available

4.1.2 Anhedonia as a constellation of reward processing impairments

Traditionally, self-report measures have focused on a loss of pleasure (e.g. Chapman, Chapman & Raulin, 1976; Fawcett, Clark, Scheftner & Gibbons, 1983) across a variety of domains (e.g. physical activities, social interactions), reflecting Ribot's (1896) original conceptualisation of anhedonia as an inability to experience pleasure. Subsequent research has, however, emphasised the multi-dimensional nature of anhedonia (see Kring & Barch, 2014; Rømer Thomsen, Whybrow & Kringlebach, 2015); which is better viewed as an umbrella term for a series of reward-processing deficits across facets of anticipation (or "wanting"), consummation (or "liking"), willingness to expend effort for reward, and reward learning, to highlight a few of the most commonly proposed domains. For example, a recent review by Pizzagalli (2014) argues that anhedonia may arise from any one (or a combination) of deficits in: the ability to estimate rewards received and a reduced expectation of future rewards; impaired ability to moderate behaviour based on reinforcement feedback; reduced willingness to expend effort to obtain rewards; and de-coupling of reward "wanting" and reward "liking". As anhedonia may arise from aberrations in any one of these components, the utility of traditional questionnaire measures, which focus solely on impairments in the ability to experience pleasure, is limited.

As this recognition of the heterogeneity of anhedonia has grown, so too has awareness that idiosyncratic impairments in specific domains of anhedonia may be differentially impaired in certain disorders. The importance of this heterogeneity is underlined by initiatives such as the Research Domain Criteria (RDoC; Cuthbert & Insel, 2013; Insel et al., 2010), which advocates for new methods of classifying mental illness by identifying discrete pathophysiological processes that are unique to certain disorders. Reward processing deficits have emerged as one of the most promising candidates for this approach and the "Positive Valence Systems" research strand encompasses work investigating the systems underlying motivational situations or contexts, including reward seeking, consummation and learning (Cuthbert & Insel, 2013). Within this strand, several researchers have argued that sub-components of anhedonia, particularly reward "wanting" or anticipatory processing, are uniquely related to the deficits in reward processing that typify unipolar (and, with an opposing profile, bipolar) depression, whereby hyposensitivity to anticipatory reward is argued to reflect

anhedonic depression, while approach-related reward hypersensitivity is argued to typify manic symptoms (Nusslock & Alloy; 2017; Treadway & Zald, 2011, 2013; Whitton, Treadway & Pizzagalli, 2015; Zald & Treadway, 2017). Thus, there is a growing interest in parsing the sub-components of reward-processing constructs, such as anhedonia.

4.1.3 Animal models of anhedonia

Evidence to support this constellation view of anhedonia has emerged from animal, behavioural and neuroimaging work, the latter two of which often demonstrate poor relationships with existent questionnaire measures of anhedonia. A complete review of the work in this area is beyond the scope of the present chapter (see Pizzagalli, 2014; Rizvi, Pizzagalli, Sproule & Kennedy, 2016 for recent, wide-ranging reviews). This section will summarise the key pre-clinical literature, which illustrates the various dimensions of reward processing and how they are masked by current definitions – and self-report measures - of anhedonia.

Animal models of depression attempt to provide quantifiable correlates of the symptoms experienced by humans. Reward processing mechanisms have been one popular target in this endeavour. Such models rely on stressors, which are either acute (e.g. tail suspension) or chronic (e.g. stressors, often unpredictable in nature, frequency and duration, including cage-overcrowding, overnight illumination etc.) in nature. In line with the model reviewed by Pizzagalli (2014), these stressors typically trigger anhedonic behaviour in rodents (for a review, see Duman, 2010). A variety of tasks have been used to assess deficits in reward processing that arise after experiencing these stressors, including: sucrose preference, place preference, intracranial self-stimulation and willingness to expend effort for reward.

In the sucrose preference paradigm, rodents are given the choice between consuming a sweet sucrose solution or drinking plain water. Preference is assessed by the volume of liquid consumed by the rodent and is typically thought to indicate hedonic tone (the ability to experience pleasure). Thus, a preference for plain water over the sucrose solution is thought to reflect anhedonia (Willner, 2005). Crucially, Willner et al. (1992) have demonstrated that this preference for sucrose-infused water versus plain water is

unrelated to calorie content and does not reflect an overall decrease in liquid consumption. Thus, the relative volume of sucrose solution (compared to plain water) is of interest. In reality, however, this paradigm reflects only consummation (or "liking") of the reward (though it could also be argued that the paradigm reflects disadvantageous decision making, i.e. in choosing to select the plain water over the more appetitive drink). Interestingly, when anti-depressant drugs such as tricyclic antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs) are administered long-term to rodents who have previously experienced chronic mild stress (CMS), the preference for the sucrose solution is restored (for a review, see Willner, 2017).

An alternative version of the CMS uses a place preference paradigm, which seeks to evaluate whether an animal shows a preference for a location in which they previously received a reward. Typically, rodents are placed in a maze or a chamber, which contains a palatable food source consistently located on one side of the space. Once the rodent becomes conditioned to expect the reward on this side of the space, the reward is removed. Healthy rodents will continue to show a bias for the previously-rewarded side of the space, even in the absence of the reward. In contrast, animals with a depressive phenotype, including those exposed to CMS, do not illustrate this preference or bias for the reward-related space. Rodents exposed to CMS, who are subsequently treated with antidepressants, exhibit a place preference for a sucrose solution (Willner et al., 1992), suggesting attenuation of the depressive phenotype with antidepressant treatment.

Finally, effort expenditure for reward paradigms have been used to evaluate willingness to exert – typically physical – effort to obtain rewards. Several variations of this design exist (see Salamone & Correa, 2018 for an overview), but the premise usually involves presenting lab animals with a choice between freely-available, low palatable food or exerting physical effort (e.g. by pushing a lever) to obtain a preferred food (e.g. Randall, et al., 2015; Salamone et al., 2007). Using such models, the impact of pharmacological attenuation of dopamine on willingness to expend effort for rewards, has been demonstrated (see Salamone, Correa, Yohn, Lopez Cruz, San Miguel & Alatorre, 2016, for a review). Crucially, several conditions hypothesised to contribute to the evolution of depressive behaviour in humans, e.g. stress and inflammation, have been shown to impair effort-related behaviour and to cause a reduction in the willingness to expend

physical effort to obtain palatable rewards (e.g. Nunes et al., 2014; Shafiei, Gray, Viau & Floresco, 2012).

4.1.4 Human analogues of pre-clinical models

Taken together, this animal research illustrates that, at the very least, we can parse separable aspects of reward processing into motivational (e.g. effort expenditure tasks), consummatory (e.g. sucrose preference tasks), and learning (e.g. place preference tasks) facets. Attempts to map these aspects of reward processing in humans have focused on creating human analogues of these animal tasks. Due to space limitations, this chapter will focus on one task, which has received a great deal of attention in the literature, however, the points raised in this section can be generalised to other task measures of anhedonia (a discussion of many such tasks is provided by Pizzagalli, 2014).

The Effort Expenditure for Rewards Task (EEfRT; Treadway et al., 2009) has been fully described in chapter 2; briefly, this task draws on the work of Salamone et al., (2007) to quantify human willingness to expend relatively greater physical effort for a larger financial reward (or, conversely, less physical effort for a smaller pay-off). Participants are offered a choice between an "easy" and a "hard" version of the task. In the "easy" task, they must use the index finger of their dominant hand to press a button 30 times within 7 seconds. If they succeed, they receive a small, fixed sum of money (depending on a prior and accurately described probability of reward receipt). In contrast, for the same probability of reward receipt, participants can opt to obtain a higher value reward by expending more physical effort, i.e. by using the "pinkie" (little) finger of their non-dominant hand to press a button 100 times in 21 seconds.

The EEfRT has been used with a variety of populations, e.g. patients with depression, schizophrenia, bipolar disorder, obesity, as well as healthy controls. Frequently, however, these studies do not incorporate a self-report measure of anhedonia. This is troubling, as much of the literature exploring the relationship between effort expenditure paradigms and self-report measures of anhedonia yield conflicting findings. The original EEfRT study, conducted by Treadway et al. (2009), in healthy participants, indicated that the Chapman Anhedonia scales significantly predicted willingness to choose the hard task when the likelihood of reward receipt was 50%. In

contrast, the Snaith Hamilton Pleasure Scale (SHAPS) was unrelated to performance on the EEfRT. While some research exists to support this observation (e.g. Barch, Treadway & Schoen, 2014), the finding does not always replicate. Yang et al. (2014) investigated EEfRT performance and self-reported anhedonia in four samples: participants with sub-syndromal depression, those experiencing a first major depressive episode, patients with remitted depression and healthy controls. They found that Chinese translations of both the SHAPS and the Temporal Experience of Pleasure Scale (TEPS) were associated with hard task choice on the EEfRT. Moreover, they also found that this relationship differed, depending on whether patients were sub-syndromal, experiencing their first episode of MDD, had remittent depression or were healthy controls. Specifically, for sub-syndromal participants, both anticipatory and consummatory pleasure (assessed by the TEPS-CON subscale) were reduced, however, reductions in anticipatory pleasure alone were associated with hard task choices and only when the likelihood of reward receipt was 80% (note: the 80% probability level they used is different from the 88% level typically specified by the EEfRT paradigm). In contrast, neither the TEPS nor the SHAPS were associated with EEfRT task choice for healthy controls, irrespective of the level of probability. For patients experiencing their first episode of depression, both the anticipatory and consummatory scales of the TEPS predicted hard task choice under 50% likelihood of reward receipt, meanwhile, only the consummatory scale was related to EEfRT performance in the 80% probability condition. Given that the SHAPS is primarily a consummatory measure, which has not previously been linked to EEfRT performance, this relationship between TEPS-CON and performance on the EEfRT is somewhat surprising. Finally, the SHAPS, but neither of the TEPS scales, were found to predict choice of the hard task on the EEfRT when the task was performed by patients with remittent depression, under a 20% likelihood of reward receipt (note: this 20% of reward receipt was substituted in lieu of the more typical 12%).

Related literature using the EEfRT (e.g. Geaney, Treadway & Smillie, 2015) reports an association between the anticipatory subscale of the TEPS (TEPS-ANT) and EEfRT task performance for healthy participants, though only when the likelihood of reward receipt is low (12%). In patient populations, McCarthy, Treadway, Bennett & Blanchard (2016) and Treadway, Bossaller, Shelton & Zald (2012) both observed unexpected patterns of findings in patients with schizophrenia and depression

respectively. McCarthy et al. (2016) report a positive relationship in patients with schizophrenia between willingness to expend effort for reward on the EEfRT and higher scores on the Motivation and Pleasure subscale (MAPS) of the Clinical Assessment Interview for Negative Symptoms (CAINS). Specifically, within patients with schizophrenia, those with more severe negative symptoms made more hard task choices on the EEfRT when the probability of reward receipt was 88% and the reward magnitude was high ($3.01 - $4.12). Similarly, Treadway et al. (2012) reported in clients with depression that higher scores on the Beck Depression Inventory (BDI-II) were associated with increased high effort plus high reward choices on the EEfRT. Exploring this finding post-hoc, they conducted an item-level analysis for BDI-II items related to reward anticipation and consummation. Based on this, they concluded that anticipatory pleasure was associated with reduced willingness to expend effort for reward, whereas increased consummatory pleasure predicted more high effort plus high reward choices. Finally, recent work by Lopez, Gamundi and Wardle (2018) suggested no relationship between anhedonia (as assessed by the anhedonia subscale of the BDI-II) and effort expenditure on either the original EEfRT or a cognitive effort adaptation.

Owing to limitations of space, not all tasks ostensibly assessing anhedonic behaviour can be discussed here. However, examples of inconsistent patterns of the relationships between self-report measures of anhedonia and behavioural analogues permeate other literatures, e.g. using variants of the chocolate milkshake task, a human analogue of sucrose preference liking tasks in animals, devised by McCabe, Mishor, Cowen and Harmer (2010). Rzepa, Fisk & McCabe found no relationship their variant of the chocolate milkshake task and either the TEPS or the SHAPS. They report a significant relationship between this task and the FCPS, but this relationship does not appear to survive correction for multiple comparisons (although the precise number of correlations run is difficult to determine).

This haphazard pattern of findings illustrates two important points that permeate much of the literature on anhedonia (and individual differences more broadly). First, frequently, no correction for multiple comparisons is reported by researchers (e.g. Rzepa, Fisk & McCabe, 2017; Yang et al., 2014). Although the latter paper comprises two separate studies, each study reports at least 24 individual correlations, in addition to the Generalised Estimating Equations (GEEs) used to analyse the EEfRT data. Apart

from a small number of studies, this absence of correction for multiple comparisons is rife in the literature, almost certainly leading to false positive findings and undermining our confidence and reliability in existent research (see Ioannidis, 2005, for a more in-depth discussion). Second, the use of a plethora of existent questionnaires, ostensibly measuring the same construct leaves researchers open to inadvertent p-hacking.

Behavioural measures of anhedonia are relatively new compared with the self-report literature. The use of multiple self-report measures to assess different aspects of anhedonia in the same study, suggests a need for a dimensional scale that taps the constellation of anhedonia suggested by pre-clinical animal models. The development of such a measure would both facilitate development and refinement of behavioural tasks, allowing for the triangulation of behavioural, neural and self-report measurements of the same construct, and allow for improved precision in the diagnosis of hedonic deficits in depression. Given the weak and inconsistent relationships emerging from studies examining the association between behavioural tasks assessing aspects of reward processing (e.g., effort expenditure for reward), the initial studies (chapters 2 and 3) were conducted in an attempt to establish convergent validity between diverse measures of approach / withdrawal motivation. The results of these studies, when viewed in the context of broader inconsistencies in the literature pointed to the need for a dimensional self-report measure of anhedonia. Thus, the decision was made to attempt to construct a new self-report measure during this programme of doctoral research, sensitive to the broader constellation of anhedonic features suggested by pre-clinical research.

4.1.5 Existent self-report measures of anhedonia

Self-report scales are the most commonly used measures of reward processing deficits, particularly in clinical settings. In contrast to behavioural or neural methods, these scales are useful in providing a direct measure of the individual's experience and have the additional advantage of being inexpensive and quick to administer. As already noted, existent questionnaires assessing anhedonia are, however, hampered by their inability to dissociate separable aspects of reward processing. This limits insight into the specific domain of anhedonia impacted in the individual (Rizvi, Pizzagalli, Sproule & Kennedy, 2016). As noted in section 5.1.2, self-report measures of anhedonia have

focused traditionally on the consummatory aspect of reward processing. The four "first-generation" questionnaires do this. These are: The Chapman Physical Anhedonia Scale, the Chapman Social Anhedonia Scale (both - Chapman et al., 1976), the Fawcett-Clark Pleasure Scale (FCPS; Fawcett et al., 1983) and the Snaith Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995).

4.1.5.1 "First generation" self-report measures

Each of these scales differ with respect to the specific aspects of anhedonia they aim to measure. The Chapman Physical and Social Anhedonia Scales were first proposed by Chapman et al. (1976) and were designed to assess trait differences in physical and social anhedonia in schizophrenia. If anhedonia is to be viewed as a putative marker for depression, scales such as these proposed by Chapman et al. (1976), which tap individual differences, are likely to be of much greater utility than state-based measures, such as the FCPS or SHAPS. However, the weak correlational relationships emerging between the Chapman scales and measures of depression severity (e.g. Leventhal et al., 2006) undermine the utility of this measure as a marker for depression. The paucity of evidence for this association likely reflects the development of these scales for use in the context of schizophrenia. The Chapman scales have also been criticised for their inclusion of items that do not clearly relate to anhedonia (e.g. *"My emotional responses seem very different to those of other people"*) and for cultural bias in the content of certain items (e.g. *"I find organ music dull and unexciting"*).

Similar criticisms can be extended to the FCPS. This state-based measure assesses anhedonic experiences in the present moment, which may be better placed to capture the severity of anhedonia during a depressive episode than as a marker for susceptibility to depression. In-keeping with this notion, the FCPS can detect acute changes in hedonic tone (e.g. Willner, Hale, & Argyropoulos, 2005). The FCPS suffers from similar cultural bias to the Chapman scales, e.g. *"You are skiing down a mountain very fast while still in good control of yourself"*, which limits its generalisability. Finally, the FCPS asks participants to imagine the pleasure they would obtain from a series of 36 scenarios. Many of these scenarios are complex, culturally-biased and hypothetical, e.g. *"While fishing, you feel a tug on your line and watch a 6-pound fish jump out of the water with your bait in its mouth" or "While raking leaves on a beautiful autumn*

day, you pause to watch your children playing in the leaf-piles." These items require both the ability to imagine a relatively complex scenario and to anticipate your emotional response to this situation. This latter requirement – affective forecasting – is particularly problematic. People are generally poor in their ability to estimate how much they will enjoy a future reward (e.g. Wilson & Gilbert, 2005) and individuals with depression or schizophrenia seem to find this task particularly challenging (Strauss & Gold, 2012; Treadway & Zald, 2013). In fact, patients with schizophrenia and depression tend to underestimate their hypothetical enjoyment of a future reward, whereas no significant group differences exist between their ratings of in-the-moment consummatory pleasure relative to controls (Barch & Dowd, 2010; Strauss & Gold, 2012; Treadway & Zald, 2011; 2013). On the other hand, research considering the psychometric properties of the FCPS tend to report good predictive validity, e.g. in its ability to distinguish depressed patients from healthy controls (Berlin, Givry-Steiner, Lecrubier & Puech, 1998) and from patients with schizophrenia (Berlin et al., 1998), as well as good convergent validity with measures of depression and discriminant validity from measures of anxiety (Leventhal, Chasson, Tapia, Miller & Petit, 2006).

Similar to the FCPS, the SHAPS (Snaith et al., 1995) emphasises state consummatory pleasure. Unlike the FCPS and the Chapman scales, the SHAPS was deliberately designed to avoid cultural bias. While this neutrality increases its generalisability, it produces some very bland statements, which some critics (e.g. Rizvi et al., 2016) argue cannot conjure up strong hedonic feelings in participants, e.g. *"I would enjoy my favourite meal"*. Despite such criticism, the SHAPS shows strong psychometric properties and has demonstrated good reliability and validity in an outpatient sample with MDD (Nakonezny, Carmody, Morris, Kurian & Trivedi, 2010), echoing previous findings in healthy adults (Leventhal et al., 2006). Although frequently used in research, the SHAPS is hampered by its focus on consummatory aspects of pleasure and its failure to correlate with physical responses to reward consummation (e.g. Rzepa, Fisk & McCabe, 2017). Finally, despite being a state measure, recent work by Langvik & Borgen Austad (2018) has emphasised the stability of SHAPS scores over time (at 10-week follow-up, $r = .71$). This result underscores the trait-like nature of anhedonia and emphasises the need to view the concept as a trait rather than a state-like symptom. Langvik and Borgen Austad (2018) also questioned the single factor structure of the SHAPS, suggesting instead that a two-factor model, comprising physical and social

anhedonia, may be a better fit. Finally, the authors explored facet-level relationships between anhedonia and extraversion, as well as other personality factors, and emphasised the importance of using these relationships to better characterise the multi-dimensional nature of anhedonia.

4.1.5.2 "Second generation" self-report measures

As recognition of the heterogeneous nature of anhedonia has grown through research such as that by Langvik and Borgen Austad (2018) and the pre-clinical models discussed in section 4.1.3, researchers have attempted to refine self-report measures of anhedonia to better reflect the multi-dimensional nature of the construct. In the past 12 years, at least seven new scales assessing anhedonia, apathy or relevant sub-components of these symptoms, have been developed (see table 5.1. for a summary). In contrast to the "first generation" questionnaires discussed above, these new measures commonly show either a more complex factor structure (representing different aspects of hedonic experience) or attempt to assess a specific sub-component or specific domain of anhedonia (e.g. social anhedonia).

4.1.5.2.1 The Temporal Experience of Pleasure Scale

The Temporal Experience of Pleasure Scale (TEPS; Gard, Gard, Kring & John, 2006) is the most widely-used of the "second generation" self-report measures of anhedonia. The TEPS is an 18-item scale, which comprises two factors, designed to assess anticipatory ("wanting") and consummatory ("liking") aspects of anhedonia. Originally developed in a healthy student sample, the scale assesses individual differences in these domains of hedonic experience. Although this scale has been widely cited and adopted for use in clinical populations with schizophrenia (Gard, Kring, Gard, Horan & Green, 2007), bipolar disorder (Tso, Grove & Taylor, 2014), opioid addition (Garfield, Cotton & Lubman, 2016) and depression (Li et al., 2015), the factor structure has been subject to criticism (see Garfield, Cotton & Lubman, 2016; Ho, Cooper, Hall & Smillie, 2015) and demonstrates variance across cultures, e.g. the Chinese version of the TEPS yields a four-factor structure (Chan, Shi, Lai, Wang, Wang & Kring, 2012), though this difference may be attributable to differences in sample characteristics or language, rather than cultural differences per se. In contrast, the two-factor solution has

demonstrated reasonable robustness in German (Simon et al., 2018) and French (Favrod, Ernst, Giuliani & Bonsack, 2008) translations, albeit with smaller than average sample sizes. Geaney, Treadway and Smillie (2015) suggest that the anticipatory subscale of the TEPS is a good predictor of willingness to expend effort for reward (as assessed by the EEfRT; Treadway et al., 2009), particularly under conditions of low likelihood of reward receipt. This finding is echoed in work by Yang et al (2014) using the Chinese translation of the TEPS (although Yang et al. do not clarify whether one or both anticipatory factors in the Chinese TEPS predict EEfRT performance).

Prior work from our own lab (Cooper, Duke, Pickering & Smillie, 2014) suggests a relationship between the anticipatory subscale of the TEPS with an EEG index of reward processing; the feedback related negativity (FRN). The FRN is an event related potential (ERP), which occurs approximately 200 – 300 milliseconds post stimulus and putatively reflects the phasic dopaminergic response to unpredicted rewards and non-rewards. Specifically, the FRN is a negative deflection in the EEG signal that occurs when the individual's expectation of reward is violated, e.g. when they expect a reward and do not receive one. A less negative (sometimes even a positive) EEG deflection occurs when an unexpected reward occurs. Thus, the FRN difference wave (i.e., amplitude on unexpected reward trials minus amplitude of unexpected non-reward trials) can be viewed as a neural index of reward prediction error or reward anticipation. Cooper et al. (2014) report larger FRN difference waves among individuals with higher self-reported TEPS ANT scores (relative to participants with lower TEPS ANT scores). The sample correlation was +0.39 (N=38). In contrast, neither the TEPS CON, nor any of the BAS subscales were related to the FRN. This association provides some validation for the dissociation of anticipatory and consummatory pleasure, however, caution is advised in interpreting these findings, given the low sample size (N = 38). In contrast, the consummatory subscale of the TEPS does not always yield convincing construct validity (see Geaney et al., 2015; Ho et al, 2015). Thus, despite its wide use in anhedonia research and the desirability of the attempt to represent different aspect of anhedonia, additional validation studies of the TEPS are required.

4.1.5.2.2 The Motivation and Pleasure Scale

The Motivation and Pleasure Scale (MAP-SR; Llerena, Park, McCarthy, Couture, Bennett & Blanchard, 2013) was derived from the Clinical Assessment Interview for Negative Symptoms (CAINS; Forbes, Blanchard, Bennett, Horan, Kring & Gur, 2010) in Schizophrenia. As such, the scale was developed in a patient population, comprising individuals experiencing schizophrenia or schizoaffective disorders. The MAP-SR yields a four-factor structure from 15 items, sensitive to anhedonia in the areas of: 1) work / recreational – and 2) social – pleasure, 3) motivation toward intimate relationships and 4) willingness to expend effort to engage in activities. While this questionnaire has demonstrated good construct validity and a stable factor structure cross-culturally (Engle & Lincoln, 2015; Kim et al., 2016), to the best of our knowledge, no normative data currently exist for this measure. Thus, it is not yet clear whether the MAP-SR can be adapted for use in individuals with depression or if it is sensitive to individual differences in hedonic tone. On the other hand, moderate correlations have been observed between total scores of the MAP-SR and the allocation of visual attention toward emotional faces. Specifically, participants with schizophrenia who report lower levels of anhedonia, allocate greater attention toward positive emotional stimuli (Jang, Park, Lee, Cho & Choi, 2015). The validation of self-report measures with behavioural tasks is encouraging, but further work is needed to consider the psychometric properties of the MAP-SR and its sensitivity to individual differences in anhedonia.

5.1.5.2.3 The Specific Loss of Interest and Pleasure Scale

The Specific Loss of Interest and Pleasure Scale (SLIPS; Winer, Veilleux & Ginger, 2014) has been designed to assess recent loss of interest or pleasure (over the past two weeks), arising predominantly from social interactions. The SLIPS comprises 23 items loading onto a single factor. The SLIPS consistently demonstrates high reliability (assessed by Cronbach's alpha) (0.94; Winer, Veilleux & Ginger, 2014; Zielinski, Veilleux, Winer & Nadorff, 2017), and has shown good convergent validity via correlations with the SHAPS and TEPS-ANT (though not the TEPS-CON; Winer, Veilleux & Ginger, 2014). The scale has primarily been used to demonstrate the predictive utility of anhedonia for suicidal ideation and attempt (e.g. Ducasse et al.,

2017; Zielinski et al., 2017). Some attempts have also been made to incorporate the SLIPS into behavioural studies of anhedonia. Bryant, Winer, Salem and Nadorff (2017) reported that anhedonia, as measured by the SLIPS, is associated with performance on the EEfRT (Treadway et al., 2009), albeit in quite a complex manner. They considered the interaction between anhedonia and "action orientation", i.e. the tendency to upregulate positive affect to aide in moving past challenges or difficulties, on EEfRT performance. The results of this study suggested that, for individuals with lower levels of anhedonia, action orientation was associated with willingness to expend effort for reward – potentially acting as a protective factor against anhedonia. However, for those participants with higher levels of anhedonia, action orientation was unrelated to EEfRT performance. It is unclear why social anhedonia, specifically, would be important for this relationship and this is not convincingly justified by the research. Beyond this study, limited work has sought to validate the SLIPS with either behavioural or neuroimaging measures, nor has there been much investigation of the psychometric properties of the measure. Overall, the one-factor solution is limiting, as is its focus on the sub-domain of social anhedonia. Finally, the emphasis on the two-week time scale is questionable, particularly in light of the lack of consensus on the stability of anhedonia over time (Rizvi et al., 2016).

5.1.5.2.4 The Anticipatory and Consummatory Interpersonal Pleasure Scale

The Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS; Gooding & Pflum, 2011; 2014a) is a 17-item scale, which focuses on social anhedonia. Although originally developed to distinguish between anticipatory and consummatory aspects of social engagement, these factors are not reflected in psychometric studies of the measure (e.g. Gooding & Pflum, 2014a). Rather, the scale yields three complex factors, each comprising a mix of anticipatory and consummatory items: intimate social interactions; group-based social interactions; and social bonding / connecting with others. Notably, this factor structure does not always replicate and a four factor structure (which includes "family-related interactions" as an additional factor) has also been reported (Gooding & Pflum, 2014b). This inconsistency in factor structure is echoed in translations of the scale into Spanish (replicates the three factor structure: Gooding, Fonseca-Pedrero, Pérezde Albézde, Sierra & Paino, 2016) and into Chinese (replicates the four factor structure: Chan, Yang, Li, Xie & Gooding, 2016). Despite

the clear construct overlap between the ACIPS and the Chapman Social Anhedonia Scale (CSAS), the original validation study revealed only a modest correlation between the two measures (-0.56). A similarly sized relationship was observed for the TEPS-CON (0.49), however, the relationship with the TEPS-ANT appeared to be quite strong (0.70), suggesting that this scale may lean more toward anticipatory pleasure than is typically recognised. As the scale is designed to be sensitive to pre-clinical deficits in social pleasure (as a marker for schizophrenia), it appears sensitive to individual differences and demonstrates good test-retest reliability (0.78) over a six- to eight- week period. Arguably reflecting these individual differences, Gooding, Padrut & Pflum (2017) report relationships between NEO domain level big five traits and total scores on the ACIPS. Predictably, extraversion yielded the strongest correlation with the ACIPS (~.60), however, all measures, except Openness, revealed weak correlations with the ACIPS (*r*s between -.23 to .34). Pro-social orientation was also one of the strongest predictors of scores on the ACIPS (after gender, positive affect and sociability). The measure has been adapted for wider use in healthy adolescents (Gooding, Pflum, Fonseca-Pedrero & Paino, 2016) and people with autism (Novacek, Gooding & Pflum, 2016), although, to our knowledge, it has not been validated in samples with, or at risk of, depression. Similarly, there is a dearth of research attempting to validate the ACIPS with behavioural measures.

4.1.5.3 Self-report scales assessing wider aspects of anhedonia

In addition to the measures discussed above, all of which explicitly assess anhedonia, several self-report measures exist, which capture various aspects of reward processing and motivation. This section will discuss two of the most relevant measures from this literature.

4.1.5.3.1 The Behavioural inhibition / behavioural activation scales (BIS / BAS)

The BIS / BAS scales (Carver & White, 1994) are arguably the most famous self-report measures of reward processing. The scales comprise 24 items and were developed to assess personality facets linked to the original reinforcement sensitivity theory (RST; Gray, 1972. Gray (1972) posited three neural systems underlying motivated behaviour: The Behavioural Approach System (BAS); the Behavioural Inhibition System (BIS)

and the Fight, Flight, Freeze System (FFFS). Of these systems, the BAS is most relevant to the present literature. The BAS scale supposedly captures affective-motivational differences in responses to rewarding stimuli and encompasses three sub-scales: Fun-seeking (FS), Drive (D) and Reward Responsiveness (RR) (though a two-factor structure has also been proposed; see Smillie, Jackson & Dalgleish, 2006). Despite its popularity, several criticisms of the BIS / BAS scales should be noted. First, the scales correspond to the original – and outdated – reinforcement sensitivity theory (oRST). Gray and McNaughton (2000) revised the RST (rRST) to account for more recent findings from animal studies of the neurobiology of anxiety. While the BAS has been minimally impacted by the revised theory, considerable changes have been made to the BIS and FFFS (see Smillie, Pickering & Jackson, 2006 for a concise discussion of the main changes). Despite this criticism and the introduction of several psychometric measures reflecting the rRST (e.g. Corr & Cooper, 2016; Reuter, Cooper, Smillie, Markett & Montag, 2015), the BIS / BAS scales remain a commonly-used measure. Second, the majority of studies adopting the BAS subscale use only the total BAS score and do not distinguish between the three subscales of the BAS. This is problematic, as it may mask important relationships in the data, possibly accounting for the lack of substantial relationship observed between BAS scores and other related measures, such as left frontal asymmetry (e.g. Wacker, Chavanon & Stemmler, 2010). Specifically, Heym, Ferguson and Lawrence (2008) report possible suppressor effects between the BAS-RR and BAS-FS, due to the differing directions of these relationships with aspects of Eysenck's Giant Three model (Eysenck, 1967).

Within the anhedonia literature, BAS is relevant, as it arguably captures several dimensions of anhedonia overlooked by traditional, first-generation, measures, e.g. BAS-RR assesses motivation to persevere to obtain a reward, which has clear overlap with anticipatory motivation and willingness to expend effort for reward. Indeed, total BAS scores have correlated modestly (.36) with hard task choices on the EEfRT (Treadway et al., 2009), under conditions when reward receipt is unlikely (12%; Geaney, Treadway & Smillie, 2015). This relationship was marginally stronger than that between EEfRT performance and the TEPS-ANT (.25), TEPS-CON (.178, non-significant) and SHAPS (.115, non-significant). The total BAS subscale shows small to moderate correlations with these anhedonia measures (.47 with TEPS-ANT; .34 with TEPS-CON; and .2 with the SHAPS; Geaney, Treadway & Smillie, 2015, though not

all these relationships were replicated in chapter 2 of the present thesis). The BAS-RR demonstrates a stronger relationship with measures of anhedonia, e.g. the ACIPS (.46), relative to the BAS-FS (.31) or BAS-D (.15) (Gooding & Pflum, 2014). Despite this, it is relatively rare for research in the area to distinguish between sub-scales of the BAS.

4.1.5.3.2 Self-report scales assessing apathy

Apathy and anhedonia both reflect deficits in motivation related to a range of psychophysiological disorders, e.g. Parkinson's Disease, Depression, Schizophrenia. Despite clear overlap between these constructs and the lack of successful therapies to treat motivational deficits, different terminologies are applied to different patient groups, with the result that these literatures have evolved largely independently (for a discussion of the overlap between these disorders, see Husain & Roiser, 2018). Several self-report measures of apathy exist, e.g. the Apathy Evaluation Scale (Marin, Biedrzycki & Firinciogullari, 1991) and the Lille Apathy Rating Scale (Sockeel, Dujardin, Devos, Denéve & Defebvre, 2006). However, only one scale has been explicitly developed to assess individual differences in apathy: The Apathy Motivation Index (AMI; Ang, Lockwood, Apps, Muhammed & Husain, 2017). The AMI is an 18-item scale, which shows reasonable psychometric properties and yields a three-factor structure: Behavioural activation, e.g. *"I get things done when they need to be done, without requiring reminders from others"*; Social motivation, e.g. *"I start conversations without being prompted"*; and Emotional Sensitivity, e.g. *"I feel awful if I say something insensitive"*. The AMI demonstrates a weak relationship with the Beck Depression Inventory (BDI; 0.26) and a moderate relationship with the SHAPS (-0.46, with the strongest association emerging for the social motivation subscale).

4.1.6 The need for a dimensional measure

As discussed above, the relationships observed between self-report measures and behavioural measures of anhedonia are typically weak and inconsistent. McCabe (2018) argues that this may be attributable to the relative insensitivity of self-report measures and behavioural measures to subtle individual differences (as observed in neuroimaging studies) in these complex constructs. While this argument should be balanced by criticisms of, e.g. the superfluity of false positives and small sample sizes

in neuroimaging research (see Button, Ioannidis, Mokrysz, Nosek, Flint, Robinson & Munafo, 2013), the need to refine the measurement of anhedonia is clear. Given pre-clinical work establishing distinct domains of reward processing, e.g. reward anticipation, willingness to expend effort, reward consummation and learning (see Pizzagalli, 2014), a clear need exists for a self-report measure that can dissociate these domains of reward processing. To compensate for the absence of such a measure, current studies typically utilise a myriad of measures to assess different aspects of anhedonia (e.g. Rzepa, Fisk & McCabe, 2017; Treadway et al., 2009). As discussed in section 5.1.3, this undermines confidence in the reliability of research, given the well documented prevalence of issues such as p-hacking and the failure to correct for multiple comparisons

4.1.7. Aims and hypotheses of the current study

Considering these issues, the first psychometric study aimed to develop a new self-report measure of trait anhedonia, sensitive to the multi-dimensional nature of this construct. An exploratory factor analysis (EFA) was planned to analyse the factor structure of the list of unique items derived from existent questionnaires assessing anhedonia and approach motivation. To truly reflect current understanding of anhedonia, this measure should represent discrete dimensions of reward processing, e.g. willingness to expend effort, anticipatory pleasure etc. Based on the unconvincing relationships observed between existent measures of anhedonia and behavioural tasks, however, it was hypothesised that this EFA would reflect the specific experiential domains assessed by the questionnaires, e.g. food, sex, hobbies, rather than the sub-components of anhedonia these measures purport to assess. The number of factors expected was not specified in advance, however, we did predict that these factors would be logically related, i.e. based on common themes from semantic relationships, rather than assessing discrete sub-components of reward processing. A confirmatory factor analysis (CFA) was also planned as the second psychometric study. This would confirm the factor structure of the new measure in a separate sample.

4.2 Study 1: Exploratory factor analysis

4.2.1 Method

4.2.1.1 Participants

523 participants (333 female) were recruited via the website Prolific Academic (https://www.prolific.ac; see Palan & Schitter, 2018). Participants ranged in age from 19-77 (*M* = 39.94 years *SD* = 11.67 years). Participants were excluded if they met any of the following criteria: self-reported previous history of psychiatric illness; non-native English speaker; currently enrolled as a student. Participants received £1.67 for completing the survey (approximately £5 for one hour of participation). This study received ethical approval from the Ethics Committee of the Psychology Department at Goldsmiths, University of London.

Table 4.2: Sample demographics for the Exploratory (EFA) Factor Analysis

	EFA	
Age	*M* 39.94 years	*SD* 11.67 years
Gender	*Female* 333	*Male* 190

4.2.1.2 Materials

Existent questionnaire measures of anhedonia and trait approach motivation were examined for unique items assessing aspects of reward processing. For the initial EFA study, a total of 171 unique items were included in the questionnaire. A full list of these items is available in appendix C. Table 4.3 presents the questionnaires from which items were obtained. As the items selected were taken from a variety of scales with differing response scales, e.g. The Chapman scales use a True / False format, whereas the TEPS includes a seven point Likert scale, it was necessary to use a common response format for all items. A 5-point Likert scale was chosen as this is a common and familiar response format for psychological scales. Moreover, the use of multiple levels of response will be likely to give the item responses better psychometric properties e.g. allowing responses to approximate a normal distribution. In turn, this

gives the item-based factor analyses used in this chapter a greater ability to uncover stable factors (see Beaujean, 2014; Tabachnick & Fidell, 2001). The creation of a common response format also necessitated minor rewording of the items to fit the common response scale, e.g. *"You sit watching a beautiful sunset in an isolated, untouched part of the world"*, item 1 from the FCPS, became *"I would find it pleasurable to sit and watch a beautiful sunset in an isolated, untouched part of the world"*. The common response scale took the form of a 1 – 5 Likert scale, ranging from 1 = *Very false for me* to 5 = *Very true for me*.

Participants completed the GAME with the following instructions:

You are about to read a number of statements that describe people's behaviours, thoughts or feelings. Please read each statement carefully. Use the rating scale to indicate how accurately each statement describes you. Describe yourself as you generally are now, not as you wish to be in the future. Describe yourself as you honestly see yourself in relation to other people you know of the same gender and age as you. So that you can describe yourself in an honest manner, your responses will be anonymous and kept in absolute confidence.

Table 4.3: The questionnaires from which items pertaining to the GAME were obtained

Scale	Authors	Description
Revised Chapman physical & social anhedonia scales	Eckbald et al. (1982)	Two scales, totalling 101 items, assessing physical and social anhedonia in a True / False format.
Fawcett-Clark Pleasure Scale (FCPS)	Fawcett et al. (1983)	36 items on a single factor, assessing consummatory anhedonia on a 9-point scale.
BAS subscale: BIS / BAS Scales	Carver & White (1994)	BAS assesses behavioural approach using 13 items, which load onto 3 factors: reward responsivity; fun-seeking; and drive. Items are measured on a 4-point Likert scale.
Snaith Hamilton Pleasure Scale (SHAPS)	Snaith et al. (1995)	Assess consummatory pleasure, 14 items, 4-point scale.
Beck Depression Inventory II (BDI-II)	Beck et al. (1996)	Anhedonia sub-scale of the BDI-II; 4 items scale assessing anhedonia in different domains, e.g. sex, food, interpersonal relationships, on a 0-3 scale.
Temporal Experience of Pleasure Scale (TEPS)	Gard et al. (2006)	2 sub-scales, 18 items, assessing consummatory and anticipatory pleasure on a 6-point Likert scale.
Motivation and Pleasure Scale (MAP-SR)	Llerena et al. (2013)	15 items, measured on a 5-point Likert scale, assessing anhedonia in the following domains: work / recreation; interpersonal relationships; activities/ hobbies.
Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS)	Gooding & Pflum (2014)	17 items assessed on a 6-point Likert scale, which measures social anhedonia across 3 interpersonal factors.
Specific Loss of Interest and Pleasure Scale (SLIPS)	Winer et al. (2014)	23-items, assessing anhedonia in a single factor, using 4 options of relative change over a two week period.

4.2.1.3 Procedure

The survey was hosted on Qualtrics, an online platform for data collection. A URL was derived and shared via the recruitment website, Prolific Academic. Members of Prolific who met the screening criteria outlined above, were offered the opportunity to participate in the study via the link to Qualtrics. The survey could be completed in more than one sitting, however, all participants completed the survey in a single sitting. Once

the survey was completed, participants were debriefed and were required to enter a completion code via the Prolific website. Their data were checked for completion and accuracy (e.g. to ensure participants did not skip all questions or select all middle options on the Likert scale) and participants were paid via their Prolific accounts.

4.2.1.4 Statistical Analyses

The Exploratory Factor Analysis was carried out in SPSS v.22. Examination of the descriptive statistics indicated that several variables in the dataset departed from multivariate normality, despite providing an extended set of response categories in the Likert scale. The correlation table showed weak relationships between several variables in the dataset. Thus, Principal Axis Factoring was chosen as the extraction method as it does not rely on assumptions of multivariate normality (Fabrigar, Wegener, MacCallum and Strahan, 1999) and is better able to detect weak factors (Briggs & MacCallum, 2003; de Winter & Dodou, 2012). An oblique rotation (Direct Oblimin) was chosen, as the factors were expected to correlate. The solutions derived from the EFA were assessed via scree plot and parallel analysis.

4.2.1.5 Data cleaning and screening

The initial 171 items were scanned to identify any items that were commonly left unanswered. No items were unanswered across the set of questions. The items were next screened to assess their power to discriminate individual differences, thus, any item that contained 75 per cent or more of the responses on the points at one end of the scale (i.e. 1 and 2 or 4 and 5) were excluded from the pool. This led to the removal of 61 items. This number is likely to reflect the inclusion of items from clinical scales, e.g. the anhedonia sub-scale of the BDI-II. Such scales require high cut-off scores to determine clinically significant scores and are thus more likely to contain items relatively insensitive to individual differences.

The remaining 110 items were explored for their adherence to the assumptions underlying factor analysis. Data were non-normally distributed for several items, which may degrade the solution (Tabachnick & Fidell, 2001), though the use of PAF as an extraction method should be reasonably robust to this (Fabrigar et al., 1999).

Mahalanobis Distance was calculated to test for multivariate outliers. 44 variables exceeded the critical chi-square value (x^2 = *166*.41). Given the large number of multivariate outliers, the individual cases were examined using a series of linear regressions to determine individual variables driving the multivariate outliers. This resulted in the removal of an additional 15 variables (note – the majority of these variables also strongly cross loaded onto multiple factors and were also identified for exclusion via re-iteration of the solution – see section 4.2.3.3). Thus, the final scale contained 51 items.

4.2.3 Results

4.2.3.1 Sample characteristics

Table 4.4: Sample characteristics for the Confirmatory Factor Analysis Sample.

	CFA	
Age	*M* 40.07 years	*SD* 11.48 years
Gender	*Female* 124	*Male* 187

4.2.3.2 Number of factors

Kaiser's measure of sampling adequacy (KMO) was .915 for the present sample, suggesting that the data were suitable for factor analysis (Tabacknick & Fidell, 2001). A four-factor structure was the most parsimonious account of the data. The decision to retain four was based in part on the scree plot (see Figure 4.1). The characteristic "elbow" of the scree plot falls below the fourth data point (indicating the number of eigenvalues), suggesting that four factors should be retained (Cattell, 1966). Combined, these four factors accounted for 32.75% of the variance in the sample. Factor 1 (Interpersonal anhedonia) accounted for the greatest proportion of the variance (18.83%), followed by factor 2 (Negative Emotionality; 6.86%), factor 3 (Sensory Pleasure; 4.38%) and factor 4 (Drive; 2.68%). A parallel analysis was performed using Jamovi (Jamovi project, 2018) and this also indicated that four factors should be retained (see Figure 4.1), which illustrates both the scree plot and the simulation data run using parallel analysis.

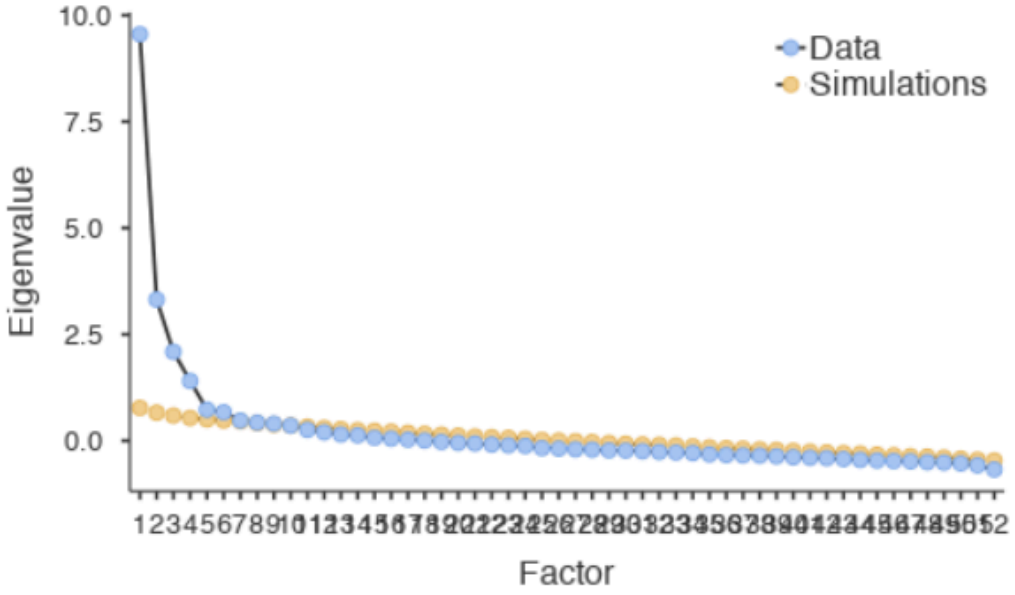

Figure 4.1 Scree plot depicting the number of factors to retain for the EFA relative to the number of factors indicated by a parallel analysis.

4.2.3.3 Item reduction

The EFA was re-run iteratively with the aforementioned settings (see section 4.2.1.4) and a four-factor solution was requested. The factor loadings of the items were then examined and any items that cross-loaded (i.e. loaded on to two or more factors) were removed. Items that loaded below 0.2 were also removed, resulting in a final scale of 51-items, which loaded on to four factors (see Table 4.5 for the complete list of items, subscales and loadings). Most of the items removed during this process were also those driving the multivariate outliers (see section 4.2.1.5). Thus, through the combination of the reiteration of the solution and the identification of multivariate outliers, 15 variables were removed. This left 51 variables in the final EFA. The factors demonstrated good reliability: Factor 1, Interpersonal Anhedonia, comprised 15 items and yielded a Cronbach's α = .902; Factor 2, Negative Emotionality, comprised 14 items and demonstrated Cronbach's α = .846; Factor 3, Sensory Pleasure, comprised 14 items and yielded Cronbach's α = .691; Factor 4, Drive, comprised 8 items and demonstrated

Cronbach's α = .689. MacDonald's Omega for the 4-factor scale was also good ω_T = 0.93.

The four factors were named according to their common themes: 1) Interpersonal anhedonia (IA): a lack of interest in / enjoyment of interpersonal relationships and activities (e.g. *I have no interest in having strong relationships with other people*; 15 items); 2) Negative emotionality (NE): a tendency to experience negative emotions, such as worry or anxiety (e.g. *I often feel blue*; 14 items); 3) Sensory pleasure: a capacity to enjoy sensory or aesthetic experiences (e.g. *I have often enjoyed the feel of silk, velvet or fur*; 14 items); 4) Drive: a thirst for sensation-seeking or achievement (e.g. *I crave excitement and new sensations*; 8 items).

Table 4.5: Goldsmiths Anhedonia Measure (GAME) – 50 items on four factors, with the associated factor loadings and cross loadings.

Statement	IA	NE	SP	Drive
I have no interest in having strong relationships with people.	**.834**	-.085	-.062	.072
Having close friends is not as important as many people say.	**.778**	-.118	.051	-.069
I attach very little importance to having close friends.	**.761**	-.049	.060	-.054
Making new friends isn't worth the energy it takes	**.710**	.098	.007	-.036
I'm much too independent to really get involved with other people.	**.702**	.007	.020	.042
I am disinterested in other people	**.652**	.107	-.065	-.022
People's daily activities and opinions are of no interest to me.	**.619**	.012	-.127	.031
There are few things more tiring than to have a long personal discussion with someone.	**.592**	-.015	-.047	.047
I have often felt uncomfortable when my friends touch me.	**.518**	.125	-.055	.013
I don't really look forward to family get-togethers or gatherings	**.483**	.178	.023	-.150
When I am alone I often resent people telephoning me or knocking on my door.	**.469**	.129	.102	-.192
I never had really close friends in high school.	**.458**	.106	.027	-.012
My relationships with other people never get very intense.	**.435**	.025	-.125	.011

I prefer watching television to going out with other people	**.432**	.083	.067	-.160
Playing with children is a real chore.	**.321**	.142	.012	.014
I often feel blue	.040	**.775**	.036	-.048
I am disappointed with myself	.051	**.741**	-.049	-.089
I have a low opinion of myself	.056	**.688**	-.023	-.060
I feel that my life lacks direction	.094	**.681**	-.020	-.133
I am critical of myself for my weaknesses and mistakes	-.056	**.598**	-.037	.095
I don't enjoy the things I used to	.179	**.590**	-.114	-.041
I find it difficult to get down to work	.130	**.588**	.034	.008
It takes extra effort to get started at doing something	.106	**.573**	-.038	.096
I put off making decisions	.069	**.561**	-.011	-.021
I don't sleep well	-.073	**.496**	.029	-.025
I get annoyed or irritated easily	.184	**.474**	-.042	.149
I worry about my health, including physical problems such as aches and pains or upset stomach and constipation	-.109	**.452**	.120	-.033
I have not lost interest in my favourite activities (R)	-.034	**-.355**	.101	.091
I have little interest in watching the types of movies I used to enjoy	.169	**.341**	-.054	.017
I have often enjoyed the feeling of silk, velvet or fur	-.028	.079	**.621**	-.026
I have been fascinated with the dancing of flames in a fireplace	.077	-.010	**.592**	-.176
On seeing a soft, thick carpet, I have sometimes had the impulse to take off my shoes and walk barefoot on it	-.039	.017	**.588**	.122
The smell of freshly cut grass is enjoyable to me	.024	-.084	**.498**	-.120
When I have seen a statue I have had the urge to reach out and touch it	-.027	.035	**.482**	.078
I really enjoy the feeling of a good yawn	.112	.001	**.423**	.088
I have never had the desire to take my shoes off and walk through a puddle barefoot (R)	.015	.111	**-.417**	.034
I have sometimes danced by myself just to feel my body move with the music	.000	.096	**.412**	.137
When I'm feeling a little sad, singing has often made me feel happier	-.082	-.015	**.356**	.149
If I discover something new I like, I usually continue doing it for a while	-.064	-.100	**.327**	.104

After a busy day, a slow walk has often felt relaxing	-.090	-.019	**.323**	.096
It is pleasurable when someone gently begins to scratch your back	-.158	.120	**.291**	.077
When eating a favourite food, I have often tried to eat slowly to make it last longer	-.088	.003	**.214**	.130
I crave excitement and new sensations	-.078	.146	.004	**.682**
I want to be the very best	-.022	-.081	-.087	**.515**
I get so excited the night before a fun event I can hardly sleep	-.079	.115	.081	**.445**
How I dress is important to me	-.048	.058	.077	**.407**
I often act on the spur of the moment	-.162	-.025	-.003	**.405**
When I'm on my way to an amusement park I can hardly wait to ride the rollercoasters	.032	-.058	.046	**.403**
I often try to lead others	-.069	-.101	.029	**.371**
You are pleased to be skiing down a mountain very fast while still in good control of yourself	.140	-.093	.083	**.328**

Note: IA = Interpersonal Anhedonia (Cronbach's α = .902); NE = Negative Emotionality (α = .846); SP = Sensory Pleasure (α = .691); D = Drive (α = .689).
Note: The original post-EFA questionnaire contained one additional item: *"I have seldom cared to sing in the shower"*. This item was removed during the CFA, as it did not load on to any factor. Bolded numbers reflect the primary loading of each item on the respective factor.

Table 4.6: Correlations between the four factors of the GAME (51-item Exploratory Factor sample)

	IA	NE	SP	Drive
IA				
r	1			
p				
NE				
r	.481**	1		
p	.000			
SP			1	
r	.259**	.063		
p	.000	.153		
Drive				
r	.347**	-.169**	.324**	1
p	.000	.000	.000	

4.3 Study 2: Confirmatory Factor Analysis

4.3.1 Method

4.3.1.1 Participants

311 participants (187 female) were subsequently recruited via Prolific Academic. These participants ranged in age from 20 - 69 (*M* age = 40.07, *SD* = 11.48). The same exclusionary criteria applied as above with the additional criterion that participants had not previously participated in the exploratory study. All participants received £1.67 (approximately £5 for one hour of participation) in return for completing the survey.

4.3.1.2 Materials

The 51-item GAME was administered to confirm the four-factor structure. The same five-point Likert scale and instructions (see section 5.2.1.2) were used. To examine the construct validity of scale, several additional measures of anhedonia and personality were administered. These included: The Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006); The Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995); The BIS / BAS scales (Carver & White, 1994) and the Big Five Inventory 2 (BFI-2; Soto & John, 2017). The TEPS, SHAPS and BIS / BAS have been described elsewhere in this chapter (see Tables 5.1 and 5.3, as well as section *4.1.5.3.1*) and so will not be discussed here. Descriptive statistics for all scales are presented in Table 4.7.

Table 4.7: Descriptive statistics for all measures included in the CFA (50 items), including mean scores, standard deviation, Cronbach's alpha and the number of items in each scale.

	Mean	**SD**	α	No. items
GAME IA	38.59	11.17	.889	15
GAME NE	39.47	9.11	.822	14
GAME SP	33.25	7.00	.699	13
GAME Drive	23.69	4.27	. 694	8
TEPS Total	77.71	11.94	.753	18
TEPS ANT	41.47	8.04	.707	10
TEPS CON	35.96	6.48	.659	8
SHAPS	1.23	1.87	.857	14

BAS Total	26.76	6.06	.878	13
BAS Fun	8.89	2.41	.758	4
BAS Reward	8.41	2.25	.739	5
BAS Drive	9.43	2.55	.838	4
BFI 2 Openness	41.64	8.45	.822	12
BFI 2 Conscientiousness	45.20	7.76	.854	12
BFI 2 Extraversion	35.41	8.25	.840	12
BFI 2 Agreeableness	44.70	7.40	.840	12
BFI 2 Negative Emotionality	31.65	8.93	.893	12

Note: IA = Interpersonal Anhedonia; NE = Negative Emotionality; SP = Sensory Pleasure; D = Drive

The GAME

The newly devised GAME (see EFA study above) was administered in this sample. This 50-item scale comprises 4 factors: Interpersonal anhedonia (IA); Negative Emotionality (NE); Sensory Pleasure (SP); and Novelty Seeking (Drive). The questionnaire response comprises a 5-point Likert scale, which ranges from 1 (*Very false for me*) to 5 (*Very true for me*). Instructions were given, as outlined in section 4.2.1.2. Note that, due to one item from the original 51-item list failing to load onto any factors, this item was dropped from the subsequent analysis. Reliabilities for the sub-scales are provided in Table 4.7.

The Big Five Inventory 2 (BFI-2)

The BFI-2 (Soto & John, 2017a) is a relatively new, validated measure of personality. It comprises 60 items assessing the five major personality traits, i.e. Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. The measure has a hierarchical structure, which encompasses 15 more-specific facets within the 5 major traits. Each item has the stem *"I am someone who…"*, followed by a brief sentence or adjective (e.g. *"I am someone who is outgoing, sociable"*). The questionnaire has a five-point Likert response scale, ranging from *disagree strongly* to *agree strongly*. Each trait has an equal number of items (i.e. 12) and there are an equal number of reverse- and true-scored items. The scale boasts good reliability and validity with an average Cronbach's $\alpha = 0.86$ for the domain trait sub-scales (Soto & John, 2017a, 2017b). Reliabilities for the sub-scales in the present sample are provided in Table 4.7.

4.3.1.3 Procedure

Once again, the survey was hosted on Qualtrics and shared via the recruitment website, Prolific Academic. The survey could be completed in more than one sitting, however, all participants completed the survey in a single sitting. Once the survey was completed, participants were debriefed and were required to enter a completion code via the Prolific website. Their data were checked for completion and accuracy and participants were paid via their Prolific accounts. This study received ethical approval from the Ethics Committee of the Department of Psychology, at Goldsmiths, University of London.

4.3.1.4 Statistical Analysis

The Confirmatory Factor Analysis was carried out using the Psych package in R. One item, *"I have seldom cared to sing in the shower"*, did not load on to any factors (it was originally the lowest loading item on the SP scale at -.214), so it was removed, leaving 50 items and four factors. Model fit was assessed using the Root Mean Square Error of Approximation (RMSEA), the Standardized Root Mean Square Residual (SRMR), and the Comparative Fit Index (CFI), in line with recommendations by Kline (2010).

The RMSEA assesses whether the specified model is a reasonable approximation of the data, with values closer to 0.0 indicative of better fit (Beaujean, 2014). Debate exists over the utility of cut-off scores to enable qualitative judgement of goodness of fit (see Lai & Green, 2016), however, the most widely used cut-offs for RMSEA suggest that values less than 0.05 (Browne & Cudeck, 1992) or 0.06 (Hu & Bentler, 1999) are indicative of a "good" fit, while values between .05 and .10 suggest "acceptable" fit (Browne & Cudeck, 1992). For the current study, the more conservative threshold of 0.05 was chosen to indicate good fit. The SRMR gives the square root of the discrepancy between the covariance matrices for the sample compared to the model. Typically, a value of .08 or lower is taken to indicate an acceptable model fit (Hu & Bentler, 1999). Finally, the CFI provides an index of the difference of fit between the hypothesised model and an independence model, which specifies zero correlation between all of the observed variables). A CFI of 0.9 is usually interpreted as an acceptable fit, with values above 0.95 indicative of a good fit (Hu & Bentler, 1999).

However, Hoekstra et al. (2011) have argued that using the independence model as a comparison will yield a lower CFI for a model with low inter-item correlations. In such instances, they suggest relaxing the CFI criterion to 0.8 for an "acceptable" fit. Given the preponderance of low correlations in the present data set, this relaxed CFI criterion of 0.8 was adopted.

4.3.2 Results

The four-factor structure of the 50-item GAME (Table 4.5) was confirmed, however, the model fit indices revealed some discrepancy in their estimates of goodness of fit. The Chi square test was significant, X^2 (896, N = 311) = 1471, $p < 0.001$, but this was expected, as this test often yields significance with larger sample sizes. Both the SRMR and the RMSEA demonstrated adequate fit (SRMR = 0.065; RMSEA = 0.054, 90% CI [0.051, 0.058]). In contrast, the CFI = 0.791, which was below even the relaxed threshold of 0.8 to indicate acceptable fit. The correlation patterns between the factors is illustrated in Table 4.8.

Table 4.8: The between-factor correlations for the 50-item GAME

	IA	NE	SP	Drive
IA				
r	1			
p				
NE				
r	.422**	1		
p	.000			
SP			1	
r	.188**	.082		
p	.000	.151		
Drive				
r	.191**	.024	.291**	1
p	.000	.679	.000	

**Correlation significant at $p < 0.01$ (2-tailed)

Cronbach's α was calculated to assess the internal reliability of each factor and of the total scale. All values were adequate ($\alpha_{overall}$ = .792, α_{IA} = .889, α_{NE} = .822, α_{SP} = .699,

α_{Drive} = .694), suggesting that the sub-scales, as well as the overall scale, had acceptable internal consistency. MacDonald's Omega was good for the present four-factor solution: (ω_T = 0.90).

To examine construct validity, correlational analyses were run between the subscale scores of the GAME and other related measures (see section 4.3.1.2 for more information). The correlation analyses were corrected for multiple comparisons so that α = 0.001 (0.05 / 52). These correlations are presented in Table 4.9.

Table 4.9: Relationship between GAME and related measures of anhedonia, approach motivation and personality

	IA	**NE**	**SP**	**Drive**
TEPS Total	-.374* .000	-.281* .000	-.593* .000	-.510* .000
TEPS ANT	-.407* .000	-.288* .000	-.373* .000	-.598* .000
TEPS CON	-.185 .001	-.160* .000	-.629* .000	-.198* .000
SHAPS	.366* .000	.263* .000	.284* .000	.215* .000
BAS Fun	.286* .000	.190 .001	.240* .000	-.554* .000
BAS Drive	.173 .002	.220* .000	.158 .005	-.459* .000
BAS Reward	.319* .000	.219* .000	.269* .000	-.443* .000
BAS Total	.300* .000	.247* .000	.256* .000	-.578* .000
BFI-2 E	-.512* .000	-.543* .000	-.319* .000	-.350* .000
BFI-2 N	.270* .000	.737* .000	.124 .029	.041 .475
BFI-2 O	-.211* .000	-.233* .000	-.400* .000	-.127 .025
BFI-2 C	-.163 .004	-.464* .000	-.062 .272	.005 .934
BFI-2 A	-.519* .000	-.349* .000	-.107 .059	-.020 .721

*Correlation significant at $p < 0.001$ (0.05 / 52). (corrected for multiple comparisons).

4.4 Discussion

4.4.1. Summary of findings

Drawing on existent measures of anhedonia and reward motivation and sensitivity, we sought to develop a new questionnaire measure, capable of assessing levels of anhedonia in the healthy population. In two separate samples, using an initial exploratory approach and a subsequent confirmatory analysis, a four-factor structure was tentatively established. An original pool of 171 items was reduced to 51 items in the exploratory analysis (and later to 50 items in the confirmatory analysis). These items loaded on to four factors, which were named based on their semantic themes: Interpersonal Anhedonia; Negative Emotionality; Sensory Pleasure and Drive. These themes were not in line with the a priori expectation that the EFA would reflect the specific experiential domains assessed by the questionnaires, e.g. food, sex, hobbies. However, these factors also do not clearly reflect the typical sub-components of anhedonia, i.e. reward anticipation and consummation (see, e.g. Gard et al., 2006).

A confirmatory analysis was run in a subsequent, separate sample and this analysis provided some tentative support for the four-factor structure. Commonly used indices of fit, including the RMSEA, SRMR and CFI, yielded slightly conflicting estimates of goodness of fit, underscoring the preliminary nature of these findings. Specifically, the RMSEA and SRMR suggested that the four-factor structure had adequate fit, whereas the CFI indicated borderline fit, even when using a more generous threshold recommended by Hoekstra et al. (2011) for models with low inter-item correlations, as in the present data.

As emphasised by Lai and Green (2016), fit indices such as RMSEA, SRMR and CFI, are continuous measures assessing different aspects of model fit. While cut-off thresholds are routinely interpreted as absolute, this interpretation is contrary to the spirit in which such thresholds were conceived, i.e. as crude aids to augment experience (Hu & Bentler, 1999; Lai & Green, 2016). Lai and Green stress that, by treating these thresholds as absolute, the indices can often provide contradictory qualitative information, making interpretation of the data difficult; as is the case in the current study. This situation can result in selective reporting of those indices that provide a more favourable account of the data, thus leading to inconsistencies and confusion in the literature (for a discussion of this, see Jackson, Gillaspy & Purc-Stephenson, 2009).

To avoid such cherry-picking, we included the most commonly reported indices of fit in the current study, but there were many additional indices that could have been included and no clear guidelines exist on best reporting in the area. Finally, it is not well understood why these indices produce inconsistencies. Pertinent to the present study, Lai and Green (2016) outline certain conditions under which the CFI and RMSEA yield conflicting estimates of fit. The data from the present CFA sample reflect those conditions outlined in case 1 by Lai and Green (2016), i.e. where RMSEA approximates 0.05 and CFI < 0.90. Under such conditions, traditional qualitative cut-offs will always yield conflicting estimates of fit. Lai and Green (2016) argue that, contrary to the typical trend in psychometric research *"the disagreement between CFI and RMSEA cannot be simply dismissed with overgeneralised, unconditional statements such as "The two indices disagree because the correlations in the data are low"* (p. 5). In lieu of relying on generic cut-offs, they argue that, while discrepancies such as those observed in the present data (i.e. RMSEA = .054; CFI = 0.79) can arise, determining the adequacy of a model fit will continue to remain challenging. Thus, researchers interested in developing psychometric measures must pay greater attention to the definition of a "good" model, rather than merely relying on arbitrary cut off thresholds to interpret their data.

One possible explanation for the observed discrepancy between the fit indices hinges on the retention of many items with low factor loadings on all four of the latent variables. The decision was made to retain all items with a loading of .2 or higher in the EFA. This is considerably below the standard (albeit arbitrary) threshold of .4 and upwards (e.g. Comrey & Lee, 1992; Tabachnick & Fidel, 2001). The weakest loading items on each scale individually explain only 4% of the variance in their respective factors. Given the low amount of variance explained by the combined four factors, these low-loading items are contributing very little to the overall measure and could potentially be excluded from future iterations of the questionnaire.

Consideration of the modification indices from the CFA indicate that several of the items could be dropped from the model to produce a better fit. These adjustments should be made and only those items that load above .4 on to their respective factors should be retained (in line with standard recommendations, e.g. Tabachnick & Fidell, 2001). This revised model should then be tested in a new sample. Refining the

questionnaire in this manner leads to the removal of a total of 10 low-loading items: one item from the IA subscale; two items from the NE subscale; five items from the SP subscale and two items from the Drive subscale. The proposed revised measure is included in Appendix D. It should be noted that this revised measure still includes several items that load below .45, particularly on the Drive subscale, which may require further refinement or may even reduce to a three factor solution. Both the revised 40-item scale and the current 50-item scale will be tested in chapter 5.

4.4.2. Relationship to models and measures of anhedonia

The four-factor solution suggested by the present study suggested anhedonic tendencies in several areas, including interpersonal (IA), emotional (NE), sensory (SP) and novelty seeking /drive (D) aspects of life. These factors differ somewhat from modern interpretations of anhedonia as a two-factor construct indicating deficits in anticipatory and consummatory pleasure, as assessed by the TEPS (Gard et al., 2006). Nor does this four-factor solution reflect the "pleasure cycle" proposed by Berridge & Kringlebach, 2013; Rømer Thomsen, Whybrow & Kringlebach, 2015 and depicted in Figure 1.1), in which the hedonic response goes through an appetitive phase, manifest in reward wanting, followed by a consummatory phase, reflected in reward liking, and finally a satiety phase, in which learning is achieved. Arguably, all these aspects of the hedonic response are reflected in the current questionnaire (e.g.: Appetitive: *"I crave excitement and new sensations"*; Consummatory: *"The smell of freshly cut grass is enjoyable to me"*; and Learning: *"If I discover something new I like, I usually continue doing it for a while"*, but these aspects load across all four factors, rather than isolating on to specific discrete factors, reflecting the hedonic cycle. As the current measure was developed from a pool of existent measures of anhedonia, the lack of a clear relationship to current conceptual understandings of anhedonia is concerning but perhaps not entirely unexpected. This suggests that typically used measures do not fully capture our understanding of the pleasure cycle, thus the gap between theory and data will continue to exist if we do not explicitly address this discrepancy by attempting to parse discrete components of rewards, e.g. anticipatory, effort, consummatory, and learning in the wording of self-report items. It should be noted that one such attempt has been made. The Dimensional Anhedonia Rating Scale (DARS; Rizvi et al., 2015)

explicitly attempted to address this issue and to create a questionnaire measure sensitive to desire, motivation, effort and consummatory pleasure. Despite this, a factor analysis of the data yielded a four-factor structure sensitive to several domains of hedonic experience, i.e. food / drink, social activities, sensory experience and hobbies. This raises doubt as to whether self-report measures are sufficiently nuanced to detect discrete phases of the reward cycle.

In contrast, the GAME's four-factor solution does show some overlap with a newly developed measure of apathy, an overlapping construct (The Apathy Motivation Index; Ang, Lockwood, Apps, Muhammed & Husain, 2017). The Apathy Motivation Index (AMI) assess individual differences in levels of apathy and motivation across three domains: behavioural activation, emotional sensitivity and social motivation. The emotional sensitivity subscale shows considerable overlap with the negative emotionality subscale of the present study, including items such as *"I feel sad or upset when I hear bad news"*. The social motivation scale also shows overlap with the interpersonal anhedonia subscale from the present study, e.g. *"I start conversations with random people"*. Interestingly, the behavioural activation subscale also shows overlap with the negative emotionality scale of the present study, including items like *"I make decisions firmly and without hesitation"* and *"When I decide to do something I am able to make an effort easily"*. This raises some questions about the integrity of the GAME Negative Emotionality subscale in the present study; perhaps it encompasses two aspects, nested within one higher order factor.

Design of this study and data collection began in September 2014. Thus, anhedonia questionnaires published since 2014 were not considered during the item generation phase of the GAME. One subsequent study is of particular interest in this respect: The Dimension Anhedonia Rating Scale (DARS; Rizvi et al., 2015). As noted above, the DARS was designed to reflect anhedonia across a range of domains, dissociated into a loss of interest / pleasure in: social activity; sensory experiences; hobbies; and food / drink. Both the social activity and sensory experience facets are also reflected in the factor structure of the GAME. This social-physical division is also reflected in the Chapman Scales (Chapman et al., 1976) and, arguably, these are the most robust factors in the present solution. This is because 1) the Negative Emotionality factor demonstrates strong overlap with the personality construct, Neuroticism (as assessed

by the BFI-2); 2) the Drive factor comprises several low-loading items. This overlap raises questions about the discriminant validity of the NE subscale of the GAME (discussed in more detail below), while the low item loadings on the Drive factor undermines our confidence in the reliability of this subscale in subsequent samples. Thus, it could be argued that the present solution really reflects the original physical / social components of anhedonia, alongside the related construct of neuroticism.

The SHAPS (Snaith et al., 1995) is frequently lauded as the "gold standard" of current anhedonia self-report measures, despite its reliance on assessing consummatory pleasure (and see a recent critique of this factor structure by Langvik & Borgen Austad, 2018). As such, the SHAPS was chosen as one of the validation questionnaires in the CFA study. Correlations between the SHAPS and subscales of the GAME were significant, but weak, ranging from .215 (Drive), to .366 (IA). It is possible that these modest relationships reflect the discrepancy between the narrow, consummatory view of anhedonia captured by the SHAPS, compared to the broad, four-factor model posited in the present study. In support of this argument, the consummatory subscale of the TEPS (TEPS CON) also demonstrated weak correlations with three of the four GAME subscales: IA (-.185, non-significant); NE (-.16); and Drive (-.198). Furthermore, the AMI (Ang et al., 2017) demonstrates relationships with the SHAPS, similar in size to those observed between the GAME and the SHAPS in the present sample. This argument is somewhat undermined, however, by the relatively robust correlations (*r*s ranging from 0.63 to 0.79) observed between the SHAPS and the multidimensional DARS (Rizvi et al., 2015). Furthermore, as recent work by Langvik & Borgen Austad (2018) suggests that a two-factor (social and physical) solution for the SHAPS may be more appropriate, we would have expected stronger convergent validity with the SHAPS and the GAME, at least between the IA and SP subscales.

As noted above, the TEPS CON yielded low, but significant, correlational relationships with most subscales of the GAME. The exception to this trend was the moderately sized correlation (-.629) between the TEPS CON and the SP subscale of the GAME, suggesting high convergent validity between the two subscales. Of the 13 items on the CFA version of the SP subscale, 2 of these were from the CON subscale of the TEPS: *"The smell of freshly cut grass is enjoyable to me"* and *"I really enjoy the feeling of a good yawn"*. When these overlapping items have been removed from both scales, the

correlation between TEPS CON and GAME SP is -.475 (significant at $p < .001$). Overall, the strength of this relationship most likely reflects the physical or sensory nature of the items on both subscales. The relationship is also not sufficiently strong to suggest the subscales are capturing an identical construct.

The anticipatory subscale of the TEPS (TEPS ANT) similarly demonstrated significant low to moderate relationships with three subscales of the GAME: IA, NE and SP (*r*s: -.407; -.288; and -.373, respectively). In contrast, a strong relationship emerged between the TEPS ANT and the Drive subscale of the GAME (-.598). This was surprising as, as noted previously, the Drive factor seemed to be the weakest and least stable factor in the solution. Of the 8 items in this subscale, 2 of them were taken directly from the TEPS ANT: *"I get so excited the night before a fun event I can hardly sleep"* and *"When I'm on my way to an amusement park I can hardly wait to ride the rollercoasters"*, which may account for some of this relationship. Indeed, once these items were removed from both scales, the correlation between the TEPS ANT and the GAME Drive dropped to -.394. The overall theme that emerges from the Drive factor is one of general striving or sensation / novelty seeking, e.g. *"I crave excitement and new sensations",* which shows clear links to an anticipatory or wanting component and may thus explain the observed relationship.

Similar to the TEPS, the BIS / BAS scales demonstrated low to moderate correlations with the subscales of the GAME. One observation is of note in this series of correlations. Namely, the relationships between all four BAS scales (BAS total and its subscales: Fun, Drive and Reward Responsiveness) and all subscales of the GAME were significant (with the sole exception of the relationship between BAS Drive and GAME-SP). Given previous research by Germans and Kring (2000), these relationships are unsurprising. The size of the relationships in the present study are broadly comparable to the observed correlation coefficients reported by Germans and Kring (2000); they noted low to moderate correlations between physical anhedonia and all subscales of the BAS, with the weakest relationship between BAS Drive and physical anhedonia (a relationship which was not significant in the present study, considering GAME SP as a proxy for physical anhedonia). These observations yield some support for the GAME as a measure of anhedonia, given the hypothesis that lower hedonic tone

will be linked to decreased responsivity to rewards and a lack of approach motivation; both of which are ostensibly assessed by the BAS scales.

What is surprising among the correlation coefficients from the present study is the strength of the relationships between GAME Drive and all subscales of the BAS (*r*s ranging from .44 to .58). According to Carver & White (1994), the subscales of the BAS each assess a different aspect of reward approach: Fun Seeking measures variance in motivation to approach new / immediate rewards; Reward Responsiveness captures differences in the anticipation of future rewards; Drive captures individual differences in persistent goal-directed behaviour. The individual items in the GAME Drive subscale can be seen to represent these different facets, e.g. "*I crave excitement and new sensations"* is an item taken directly from the Fun Seeking subscale of the BAS; "*When I'm on my way to an amusement park I can hardly wait to ride the rollercoasters"* is an item reflecting anticipatory pleasure; and "*I want to be the very best"* conceptually represents BAS drive (though it is not an item on BAS Drive). Only two items from the BAS scales are included in the GAME. These are: *"I often act on the spur of the moment*" and "*I crave excitement and new sensations*". Both these items form part of the BAS subscale Fun Seeking and part of the GAME subscale Drive. The correlation between BAS-Fun and GAME-Drive drops from $r = .554$ to $r = .296$ after removing these two overlapping items from both scales. It should be noted that, after removing these two items, BAS-Fun contains only two items and the scale reliability drops from $\alpha = .758$ to $\alpha = .665$. The observation that the GAME Drive subscale correlates strongly with disparate measures of reward anticipation and motivation raises concern over the validity of this subscale, particularly in light of observations that anhedonia is differentially impacted at various stages of reward anticipation, learning and motivation (e.g. Germans & Kring, 2000; Pizzagalli, 2014; Treadway & Zald, 2011). This observation may point to a multi-dimensional anticipatory pleasure or "wanting" stage of the reward cycle, as has recently been argued by Krupic and Corr (2017) and Zald and Treadway (2017).

4.4.3 Relationship to Big Five personality measures

Some of the strongest correlational relationships emerged between the subscales of the GAME and personality subscales from the BFI 2 (Soto & John, 2017). The Negative Emotionality (neuroticism) subscale of the BFI 2 demonstrated a particularly strong association with the NE subscale of the GAME (hence the choice of label for this subscale). Indeed, many of the items included in this subscale are in keeping with the traditional view of trait neuroticism (also known as negative emotionality to distinguish the trait from its clinical connotations; Soto & John, 2017), e.g. *"I often feel blue"*, *"I am critical of myself for my weaknesses and mistakes"*. The substantial correlation between these scales observed in the present study raises questions over the discriminant validity of this subscale and its specificity to anhedonia. Rather than representing a facet of anhedonia, this subscale may be reflective of related personality vulnerabilities, e.g. tendencies toward neuroticism or anxiety, which place one at greater risk of becoming anhedonic (Liao et al., 2019). Alternatively, this subscale may reflect overlap with another cardinal symptom of depression: low mood. The utility of a new anhedonia scale hinges on its ability to discriminate those aspects of hedonic experience from broader vulnerabilities to motivational and depressive disorders and the more general depressive symptom profile. The inclusion of a subscale sensitive to negative emotionality is arguably useful in a measure of anhedonia, particularly if it will be used in a clinical setting. Anhedonia and low mood are the two cardinal symptoms of depression. The negative emotionality subscale seems to capture central attributes of low mood. By including a measure of low mood in the GAME, it allows researchers to differentiate the respective contributions of negative emotionality and discrete aspects of anhedonia to an overall depression score, e.g. it may be possible to see the unique contribution of anhedonia to an outcome, such as stress, by considering the variance accounted for by the Drive, interpersonal anhedonia and sensory pleasure subscales, with negative emotionality partialled out. In order to substantiate this interpretation, further validation of the GAME is needed; in particular, the negative emotionality scale should be validated with a measure of depression. Care should be taken to test the discriminant validity of these scales explicitly, e.g. in their ability to predict depression, using the refined model in a separate sample (see, for example, Bodukszek & Dhingra, 2016).

Negative associations between extraversion and depression are reasonably well established (Jylha & Isometsa, 2006) and some theorists have argued that anhedonia,

in particular, may be linked to low extraversion (Clark & Watson, 1991). This relationship is reflected in the moderate negative correlations observed in the present study, between trait extraversion and all four subscales of the GAME. Unsurprisingly, the strongest of these relationships were observed a) between extraversion and interpersonal aspects of anhedonia (captured by GAME IA: r = -.512), likely reflecting the well-established facet of sociability in extraversion (e.g. Depue & Collins, 1999; Soto & John, 2017); and b) between extraversion and the negative emotionality subscale of the GAME (-.543), which likely reflects the tendency for extraverts to experience more positive (and fewer negative) emotions (e.g. McCrae & Costa, 1987; Smillie, DeYoung & Hall, 2015; Watson, Clark & Harkness, 1994; Watson & Clark, 1997; Wilt & Revelle, 2009). Weaker, though still pronounced, relationships were observed between extraversion and the Sensory Pleasure (-.319) and Drive (-.350) subscales of the GAME. Finally, the low-to-moderate negative correlation between extraversion and GAME-Drive (-.350) merits acknowledgement. This relationship is in keeping with the observed relationships between GAME-Drive and the subscales of the BAS (BAS Total: -.578; BAS-RR: -.443; BAS-Fun: -.554; BAS-Drive: -.459), given previous work on the putative overlap between extraversion and BAS (e.g. Depue & Collins, 1999; Pickering, Corr & Gray, 1999; Smillie, Pickering & Jackson, 2006). Items ostensibly tapping excitement or sensation-seeking, e.g. "*I crave excitement and new sensations"* are among the strongest-loading items on GAME-Drive, which may also account for this association, given arguments that sensation-seeking constitutes a central aspect of extraversion (e.g. Costa & McCrae, 1992; Eysenck & Eysenck, 1985; Zuckerman, 1994). The relationship between GAME-SP and BFI-2 Openness was also noteworthy (-.40) and can most likely be ascribed to the overlap between this subscale and aspects of Openness (e.g. due the overlap with aspects of aesthetic appreciation – "*When I have seen a statue I have had the urge to reach out and touch it"*).

Interest in the relationship between depressive disorders generally and anhedonia more specifically tend to focus on individual differences in extraversion and neuroticism. Trait agreeableness typically receives less attention, despite its theoretical interest, given the long-established social facet of anhedonia (e.g. Chapman, Chapman & Raulin, 1976). Trait agreeableness comprises aspects of pro-social behaviour, e.g. honesty, compassion, altruism, politeness (DeYoung et al., 2007; McCrae & Costa, 2010; Soto & John, 2017). Given Meehl's (1962) understanding of social anhedonia as

a primary deficit in the ability to find social experiences rewarding or pleasurable, it seems reasonable to suggest that people experiencing social anhedonia are less motivated to engage in agreeable, pro-social behaviours. Indeed, Silvia and Kwapil (2011) argue that social anhedonia reflects a genuine disinterest in social interactions, not merely aspects of shyness or introversion. This argument may explain the moderate relationship observed between Agreeableness and the Interpersonal Anhedonia subscale of the GAME in the present study (-.519). This relationship is stronger than those previously observed, e.g. by Kwapil, Barrantes-Vidal & Silvia (2008), in which they observed a weak correlation between social anhedonia and agreeableness (-.28) after partialing out variance associated with positive schizotypy and by Gooding, Padrutt & Pflum (2017), who observed a weak relationship (.34) between the agreeableness domain of the NEO-FFI and the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS). Though it should be noted that pro-social orientation was one of the strongest predictors of anhedonia (as assessed by the ACIPS) in this study. To our knowledge, this relationship between agreeableness and anhedonia has received little attention, particularly in relation to depression. It thus represents an area for further exploration in future work. Taken together, the observed relationships between the broad framework of the five factor model and discrete subgroupings of anhedonic experience suggest a need to further examine these relationships at the facet (or aspect) level of the big five traits in order to clarify the nature, measurement and biological framework of anhedonia (see, e.g. work by Mueller, Panitz, Pizzagalli, Hermann & Wacker, 2014).

4.4.4. Limitations of the present study

Several limitations should be acknowledged when considering these results. Firstly, the sample size in both studies is perhaps a little lower than ideal. While concrete guidelines on optimal sample size for factor analyses are lacking, rules of thumb range from at least 300 participants for an EFA (Tabachnick & Fidell, 2001) to more precise calculations, e.g. using the online sample size calculator for structural equation models, which suggests a minimum sample size of 342 to detect a correlation of .2 in the current CFA sample (Soper, 2018). While the samples in the present study broadly meet these criteria, it should be noted that the number of factors, the strength of the correlational relationships in the data and the factor loadings also influence this calculation. As noted

previously, many of the correlations in these data sets were quite low and this is reflected in the large number of low loadings on the four factors. Thus, it is arguable that a larger sample would have been preferable, particularly for the CFA.

A second limitation concerns the derivation of the original list of items. We deliberately chose a broad array of reward-related questionnaires from which to develop the present scale. We did this to ensure that oft-overlooked putative domains of anhedonia, e.g. deficits in reward wanting and learning, were fairly represented in our sample. In casting such a wide net, we may have inadvertently included several items that represent related concepts, e.g. neuroticism, as reflected in the NE subscale of the GAME, rather than anhedonia per se. In refining this questionnaire, it is crucial that the discriminant validity of the subscales – particularly the NE subscale – is ascertained. It should also be noted that this method of item generation differs from the standard lexical approach typically employed in the development of questionnaires (see, for example, Ang et al., 2017; Gard et al., 2006; Snaith et al., 1995). Ideally, our original item pool (171) would have been evaluated by independent experts in the area, outside of the research team (as per recommendations by Slavec & Drnovsek, 2012). The original list of items was also heavily biased toward social and consummatory aspects of anhedonia. This reflects the dominance of these facets in existing measures (see table 4.1). Efforts to balance the nature of these items with the other dimensions of the reward cycle may have influenced the subsequent factor structure.

A third limitation, pertaining to the EFA, involves the retention of so many low loading items on each of the four factors (i.e. items loading below .4). Items loading above .2 were retained in the initial EFA model (study 1) to maximise the explanatory power of the model. Retention of these items most likely accounts for the inconsistency between the fit estimates in the CFA study, particularly the poor CFI index, although initial CFA models typically do not fit the data very well (Kline, 2011). Closer inspection of the modification indices in the CFA suggested that the scale should be refined to remove items that load poorly and the structure of the questionnaire should be confirmed in a separate sample. Modification indices are univariate estimates of the degree of change necessary to obtain the optimal value of a fit index as constraints on the estimate change (Kline, 2011). Changes to the specification of a model should be based on a combined consideration of the modification indices and knowledge of the specific area under

study (Kline, 2011). Inspection of the modification indices combined with the factor loadings (as discussed above) suggested that the model fit would be improved if 10 items were removed. This resulted in 5 items being dropped from the SP subscale; 2 items being dropped from both the NE and Drive subscales; and 1 item being dropped from the IA subscale. A list of the items dropped is provided in Appendix E. Given the proposed improvement to the model fit, we decided to use this revised version of the GAME in the final study of programme of research, however, we collected the full 50 items to allow for the explicit comparison of model fit indices between the two scales (see Chapter 5).

Finally, some small changes should be made to the wording of the instructions to make them more clear for participants. The original instructions given to participants include the phrase *"Describe yourself as you honestly see yourself in relation to other people you know of the same gender and age as you."* Encouraging participants to compare themselves to others may conceivably bias the responses to these questions and is not commonly used with the instructions typically provided with personality or clinical scales. Finally, the phrase *"Describe yourself as you generally are now, not as you wish to be in the future"*, is an expansion on the usual phrasing employed to ensure responses relate to traits. It is conceivable that this may also have created some confusion and could be reworded. The GAME is intended to assess trait-like individual differences in anhedonia, suggesting participations should indicate how they are typically or in general. The wording *"as you generally are now"* may lead participants to conflate their state (in the moment) response with their more general behaviour. This potential confound is particularly important for anhedonia, given that it encompasses both state and trait-like aspects (for a discussion, see Shankman, Katz, DeLizza, Sarapas, Gorka & Campbell, 2014).

4.5. Conclusion

This study sought to establish a new measure of anhedonia, which taps broad facets of the construct, rather than focusing on increasingly narrow aspects of anhedonic experience (e.g. the ACIPS; Gooding & Pflum, 2014). Existent measures of anhedonia and reward processing were examined to generate a set of 171 unique items that assessed various aspects of anhedonia. An exploratory factor analysis suggested a four-

factor solution, which parsed anhedonia into Social (interpersonal anhedonia); Emotional (Negative Emotionality); Physical (Sensory Pleasure) and Novelty Seeking (Drive) aspects. These themes ran contrary to a priori expectations, i.e. that the measure would reflect broad domains of hedonic experience, e.g. the enjoyment of food, social occasions, sex etc. A subsequent confirmatory factor analysis yielded tentative support for this four factor model. It should be noted, however, that all the fit indices for this confirmatory model were not in agreement and, thus, further work is probably needed to refine and validate this measure in a new sample. The discriminant validity of one of the subscales (negative emotionality) is also questionable, given its strong overlap with trait neuroticism (as assessed by the BFI-2). Finally, moderate relationships with other Big Five traits, namely extraversion and agreeableness, point to a need to consider facet-level relationships with anhedonia to clarify these associations. Despite the limitations discussed in this section, the GAME was adopted for use in the final study of this programme of research to counter the manifold limitations of existent measures of anhedonia, as outlined in this chapter.

Chapter 5

Does a proxy measure for alpha EEG asymmetry partially mediate the relationship between anhedonia and stress?

Overview

Stress is a well-established risk factor in the development and maintenance of depression. Specifically, stress may cultivate an anhedonic depressive phenotype via stress-induced abnormalities in mesolimbic and mesocortical dopaminergic pathways. The present study aims to test whether individual differences in perceived stress differentially predicts aspects of anhedonia pertaining to social, emotional, novelty-seeking and anticipatory processes, compared to more sensory / consummatory pleasure deficits. Using a newly developed measure of anhedonia, the Goldsmiths Anhedonia Measure (GAME), self-reported perceived stress and anhedonia scores were calculated for $N = 294$ healthy, right-handed adults. Participants also completed a line bisection task as a proxy measure of frontal EEG asymmetry, a putatively dopaminergic index of approach / avoidance motivation. It was expected that leftward bias on the line bisection task (indicative of greater right cortical activity) would partially mediate the relationship between perceived stress scores and anhedonia in social, emotional, novelty-seeking and anticipatory domains. Specifically, leftward bias on the line bisection task (indicative of relatively greater right cortical activity) would be associated with both higher levels of anhedonia and greater perceived stress. Relative right cerebral asymmetry (indexed by leftward bias on the line bisection task) was also expected to mediate the relationship between perceived stress and anhedonia. As predicted, individuals with relatively greater perceived stress reported higher levels of anhedonia. This was true only for social and emotional aspects of anhedonia (i.e. the interpersonal and negative emotionality, but not the sensory or drive subscales, of the GAME). Contrary to the above predictions, the association between perceived stress and anhedonia was not mediated by performance on the line bisection task. Similarly, greater perceived stress predicted lower levels of anticipatory (but not consummatory) pleasure. These findings are discussed in relation to specific and dissociable influences of stress on the reward system and the sensitivity of the line bisection task and questionnaire measures to assess reward processing deficits.

5.1 Introduction

5.1.1 Heterogeneity in depression

Mental ill-health costs the UK economy an estimated £105 billion per annum (Sainsbury Centre for Mental Health, 2010). Depression is a leading contributor to these costs, given its high prevalence of approximately 17.8 per cent (Office of National Statistics, 2018), with estimates of major depression (MDD) ranging between 6.4 per cent for a single lifetime episode to 12.2 per cent for moderate recurrent major depression, and around 7.2 per cent for severe recurrent MDD (Smith et al., 2013). Indeed, the World Health Organisation (WHO) suggests depression will be the single largest burden of ill health worldwide by 2020 (WHO, 2001).

Despite the pronounced burden of disease poised by depression, relatively little is known about its aetiology and pathophysiology. In part, this ignorance may be due to the heterogeneity of the disorder and its idiosyncratic presentation. As noted in the introduction to this thesis, diagnosis of depression is dependent on the presentation of several broad symptoms, so that two individuals may both receive the same diagnosis and treatment, despite sharing only one common symptom, which may be as generic as fatigue or reduced appetite (Treadway & Zald, 2011). As diagnoses are based on symptom clusters and the clinical course of disease, it is all too easy to overlook the pathophysiological mechanisms driving disorders (Hyman, 2007) and, as a result, contemporary diagnostic systems may artificially group together heterogeneous sets of disorders with discrete pathophysiologies.

An increasing interest in parsing putative sub-types of disease based on brain-behaviour relationships has emerged in recent years with the introduction of initiatives such as the Research Domain Criteria (RDoC). The RDoC aims to introduce a new classification system for mental disorders, which moves away from existent taxonomies that rely on phenotypic presentations and symptom clusters, but rather, emphasises research-based knowledge about the biological mechanisms underpinning disease (see Insel et al., 2010). Heterogeneity at symptom level – often driven by unclear operationalisations of concepts such as “anhedonia” and “reward processing” are at least as problematic as the heterogeneous presentation of the disorders themselves (Treadway & Zald, 2011).

Increasingly, research points to a discrete anhedonic phenotype of depression, which is characterised by deficits in reward processing – primarily in anticipatory or "wanting" phases of the reward cycle (see chapter 1) – and which may arise from stress-induced aberrations in dopaminergic processes (e.g. Treadway & Zald, 2011; 2013; Pizzagalli, 2014).

5.1.2 Stress: a risk factor for depression

Contrary to the human focus on phenotypes of depression based on symptom clusters, animal models of depression emphasise pathophysiological mechanisms that may underlie discrete symptoms and depressive phenotypes. Specifically, these models seek to engender behavioural changes analogous to individual symptoms of psychiatric disorders. Such changes can be cultivated either through biological mechanisms (e.g. alterations of the concentration of neurotransmitters in specific neural regions through dietary or physiological mechanisms) or behavioural means (e.g. social crowding in changes or the administration of shocks). Much of this research emphasises the chronic mild stress (CMS) model of depression. Indeed, Willner (2017) reports that this model has been used in over 1,300 published studies since its inception 30 years ago.

The CMS model of depression exposes rodents to a variety of uncontrollable small-scale stressors over a series of weeks. Such stressors include: water bottles leaking into bedding; a failure to regularly re-fill food and water; unexpected alterations in the light-dark cycle of the animal's chamber; unexpected changes in housing, e.g. overcrowding, increased noise etc. Such stressors are administered constantly and unpredictably over a 5 - to 9 - week period. Exposure to these stressors leads rodents to display a range of behavioural symptoms consistent with depressive and anhedonic phenotypes in humans, e.g. a decreased appreciation for sweet tastes and an increased threshold for pleasurable brain stimulation (e.g. Moreau, Jenck, Martin, Mortas & Haefely, 1992, 1993); a reduced interest in exploratory activity and locomotion (e.g. Rygula, Abumaria, Flügge, Fuchs, Rüther & Havemann-Reinecke, 2005); impairments in place-preference conditioning for rewarding stimuli (e.g. Papp, Willner & Muscat, 1990), though not for avoiding aversive stimuli (see Papp, Lappas, Muscat & Willner, 1992); and decreases in self-care, e.g. grooming (see Isingrini, Camus, Le Guisquet, Pingaud, Devers & Belzung, 2010). Such behaviours broadly reflect depressive symptomologies,

particularly putative anhedonic deficits in aspects of reward motivation and pleasure, supporting the validity and reliability of the CMS model of depression (for discussions, see Czéh, Fuchs, Wiborg & Simon, 2016; Fernando & Robbins, 2011; Willner, 2017).

In support of the CMS model of depression, stress has been strongly implicated in both the development and worsening of depressive symptoms in humans. Approximately 80 per cent of depressive episodes are preceded by the experience of major life events, and stressors are perceived 2.5 times more frequently by patients with depression, relative to controls (Mazure, 1998). Chronic stressors predict both poorer prognosis for depression, as well as higher rates of relapse (Lethbridge & Allen, 2008). Similarly, more severe symptoms of depression have been associated with the experience of chronic stress in both patients with current and remittent depression (Leskela et al., 2006). Stressful experiences are particularly important in triggering first episode depression (Daley, Hammen & Rao, 2000), but play less of a role in subsequent depressive episodes (Kendler, Thornton & Gardner, 2000). This observation is central to the so-called "kindling-sensitization" hypothesis (Post, 1992), whereby neuroanatomical changes occurring in response to depression, sensitize an individual for subsequent depressive episodes.

Indeed, a strong body of evidence supports the kindling-sensitization hypothesis, based on observations of associations between the experience of early life stress, e.g. childhood maltreatment and the subsequent development of depression. Adversity in childhood spans a variety of domains, including emotional and physical neglect, parental death, and various forms of physical, emotional and sexual abuse. Despite differences in the nature of the adversities experienced, there is robust evidence linking early life stress with the development of depression in a dose-response manner (e.g. Green et al., 2010; Kessler, Davis & Kendler, 1997; Nanni, Uher & Danese, 2012; Norman et al., 2012; Wiersma, 2015), i.e. the more adversity experienced in childhood, the greater the likelihood of developing depression in later life. Such evidence could plausibly be interpreted as early life stressors sensitizing the individual to subsequent depressive episodes, in line with the kindling-sensitization hypothesis. Increased childhood adversity has also been linked to the experience of more severe depressive symptoms (Wiersma, 2015), particularly, heightened levels of anhedonia (Lumley & Harkness, 2007). This relationship is complex and suggests that the experience of early

life stress and the subsequent development of anhedonia is mediated by the development of an individual's schemas of worthlessness or hopelessness.

Taken together, this work suggests that stress is a key risk factor for depression. In particular, the build-up of multiple small-scale stressors seems to promote the development of a depressive phenotype linked to a loss of interest, motivation and pleasure, pointing to stress-induced deficits across the reward-processing spectrum. Such chronic stressors, when initially experienced, may sensitise the organism, leading them to underestimate their ability to control or otherwise deal with stress. The development of such a negative coping schema may then place the individual at heightened risk for the development of further depressive episodes.

5.1.3 Hopelessness and the diathesis-stress model of depression

Lending further credence to the role of stress in the aetiology of depression, several diathesis-stress models of depression have been proposed, e.g. based on the existence of a negative attribution bias (e.g. Abramson, Metalsky & Alloy, 1989; Beck, 1967, 1987). The theory underlying such models is that a strong diathesis, i.e. a trait-like bias toward, in this case, attributing negative events to stable, global causes that are uncontrollable, constitutes a vulnerability toward development of depression. Depression will develop when individuals with this diathesis are exposed to a sufficient degree of stress. These vulnerabilities interact, so that the greater the diathesis, the less stress that is needed to trigger a depressive episode. Longitudinal research has provided some support for this hopelessness diathesis. Metalsky & Joiner (1992) observed that the interaction between stress and attribution style predicted depression symptoms (but not symptoms of anxiety) over a five-week period. Specifically, participants who experienced negative life events and had an existing tendency to make negative judgements about themselves in light of negative occurrences (e.g. I failed this exam and therefore I am stupid), and / or a tendency toward catastrophizing from negative events (e.g. I failed this exam and therefore I will not graduate), demonstrated an increase in depressive symptoms. Similarly, Hankin, Abramson, Miller and Haeffel (2004; study 2) point to an interaction between these attributional biases and the experience of negative life events in predicting heightened depressive symptoms over a two-year period.

Updating the hopelessness diathesis-stress model to encompass broader psychological theory on depression (particularly Davidson's (1992) motivational direction theory; see section 1.7.1), Abramson, Alloy, Hankin, Haeffel, MacCoon and Gibb (2002) argue that the diathesis-stress model leads to the development of depression by engendering deficits in goal-directed behaviour. Specifically, those individuals who have a diathesis for depression and experience the requisite levels of stress to trigger this vulnerability, develop feelings of hopelessness. This hopelessness, in turn, leads to a reduction in approach motivation, leading to the presentation of a depression characterised by anhedonic deficits. In line with Davidson's (1992) theory of motivational direction, this diathesis stress model is mirrored in the relative dominance of the right and left cerebral hemispheres. Abramson et al. (2002) echo Davidson's position that relatively greater right (than left) hemispheric activity places an individual at increased risk of developing depression. Abramson and colleagues (2002) expand this theory by positing that the development of hopelessness in response to the experience of chronic stress paves the way for the relative dominance of right hemispheric activity.

To test the hopelessness diathesis stress model, Haeffel, Abramson, Brazy and Shah (2008) investigated a four-step mediation model, whereby the experience of stressful life events predicted the development of hopelessness, a relationship, which was mediated by the existence of a cognitive / attributional vulnerability (i.e. a tendency to construe stressful life events as having negative implications for one's self worth and the future). Hopelessness, in turn, predicted goal-directed behaviour, a relationship which was also mediated by the cognitive / attributional vulnerability. In line with the revised theory (Abramson et al., 2002), stressors interacted with the diathesis (i.e. negative attributional style) to predict decreased goal-directed behaviour. This relationship was mediated by hopelessness. Thus, in line with the observations from work using the CMS model of depression, in chronically stressful situations, a perceived lack of control is likely to interact with feelings of hopelessness or an inability to escape the situation, leading to decreases in goal-directed behaviour and approach motivation.

1.5.4 Mechanisms of action for stress-induced anhedonia

Pizzagalli (2014) argues that stress-induced dysfunction within mesocortical and mesolimbic reward pathways may be a key mechanism through which anhedonic depression develops. Reflecting the differential impact of different stressors on discrete aspects of reward processing, the mesocortical and mesolimbic dopaminergic pathways also show differential responses to different stressors, which may underlie the reward processing deficits that characterise anhedonia. Acute stressors briefly increase approach motivation, presumably elevating goal-directed behaviour to help the organism overcome a short-term stressor. In contrast – and in keeping with the hopelessness diathesis stress model put forward by Abramson et al. (2002) – chronic stress, particularly when it is perceived to be uncontrollable, reverses this effect and triggers withdrawal motivation, leading to a reduction in the organism's approach motivation and heightening its motivation to avoid the stressor (Lemos et al., 2012).

The mechanism of action for this stress-induced reversal in motivation is reliant on the activity of the corticotrophin releasing factor (CRF), a neuropeptide, which is released in response to acute stressors. The CRF acts on the nucleus accumbens (NAcc) to promote the release of dopamine (via CRF receptors: CRF1 and CRF2). Chronic stress extinguishes this effect and subsequent recovery of the CRF activity is slow. This, in turn, triggers the switch from heightened approach motivation to increased withdrawal motivation (Lemos et al., 2012). Behaviourally, this attenuation of mesolimbic dopaminergic function is linked to a depressive phenotype, characterised by despair, learned helplessness and a failure to cope in rodents (Cabib & Puglisi-Allegra, 2012), in-keeping with the hopelessness diathesis stress model. While chronic inescapable stress inhibits dopaminergic action in the NAcc, it promotes dopaminergic activity in the medial PFC (mPFC), relative to an escapable stressor of similar intensity and duration (Cuadra, Zurita, Lacerra, & Molina, 1999). Dopamine inhibits activity in the mPFC, thus, increased dopaminergic function in this region may reduce mPFC-mediated behaviour, such as the activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis (Maier, Amat, Baratta, Paul, & Watkins, 2006), which plays a key role in mediating an organism's response to stress, particularly the fight or flight response. Interestingly, previous experience of chronic stress leads to an increase in the response of the mesocortical dopaminergic pathways to an acute stressor. Arguably, this may reflect

the kindling sensitization hypothesis proposed by Post (1992). Owing to regulatory connections between the PFC and NAcc (Del Arco & Mora, 2008), it may be that stress-induced alterations in the mesocortical dopaminergic system, in turn, blunt the release of dopamine in the mesolimbic pathway, thus maintaining reward processing alterations, leading to an anhedonic phenotype.

Prolonged exposure to chronic stress elicits lasting changes in these systems. Long-term neurophysiological changes include downregulation of mesolimbic dopaminergic systems, reduced levels of the dopamine transporter (DAT) protein (which is the primary mechanism for terminating the dopamine signal by clearing it from the synaptic cleft) and sensitization of the mesocortical dopamine pathway to novel stressors (Pizzagalli, 2014). Downregulation of the dopaminergic system is illustrated through work by Moore, Rose & Grace (2001), who report a 64 per cent reduction in the amount of spontaneously active dopaminergic neurons in the ventral tegmental area (VTA) in response to a prolonged stressor (exposure to cold temperatures of 4 degrees Celsius over a 17-day period). Chronic stress also leads to a reduction in dopamine transmission in the NAcc, which mediates motivational processes. This reduction in mesolimbic dopamine appears to be closely related to difficulties in coping (e.g. a lack of escape from a stressor) and the maintenance of depressive behaviours (Mangiavacchi, Masi, Scheggi, Leggio, De Montis & Gambarana, 2001).

Chronic stress exposure is similarly linked to reduced levels of DAT in the NAcc and mesolimbic pathway, suggesting decreased dopaminergic release. This reduction has been elicited in response to a range of stressors, including early maternal separation (e.g. Brake, Zhang, Diorio, Meaney & Gratton, 2004) and chronic social stress (Lucas et al., 2004). This reduction in mesolimbic DAT has also been described post mortem in patients with depression (Klimek, Schenck, Han, Stockmeier & Ordway, 2002). Taken together, this evidence further substantiates the hypothesis that depression is linked to dopaminergic aberrations in the mesolimbic system and that these may be linked to the experience of stress.

Finally, the experience of chronic stress seems to sensitize the mesocortical dopamine pathway to novel stressors. Cuadra et al. (1999) report increased dopaminergic release in the rat frontal cortex in response to restraint stress among rodents previously exposed

to early chronic stress (relative to control animals). These results point to the sensitization of dopamine processes in the frontal cortex following exposure to a chronic stressor. Chrapusta, Wyatt and Masserano (1997) suggest that this sensitization effect is uniquely maintained in frontal cortical (but not subcortical) regions, following cessation of the novel stressor. Given the previously mentioned inhibitory regulatory influence of mesocortical dopamine on the NAcc (Del Arco & Mora, 2008), such sensitization may, in turn, inhibit approach motivation tendencies, leading to hopelessness and increased withdrawal motivation, thus maintaining anhedonic behaviour.

Taken together, this work points to a dopamine-mediated pathway through which stress may affect different aspects of reward processing. Specifically, the nature of the stressor – whether it is temporary and / or escapable versus chronic and inescapable – differentially activates the mesocortical and mesolimbic dopaminergic pathways. Acute, controllable stressors promote dopaminergic activity in the NAcc leading to heightened goal-directed behaviour, allowing the organism to cope with stress. If this stress is sustained, this mechanism is reversed, leading to a depletion of dopaminergic function in the NAcc, promoting withdrawal from the stressor or the manifestation of hopelessness and deficits in coping. In parallel, chronic stressors lead to heightened dopaminergic activity in the mPFC, which inhibits activities controlled by this region. This inhibition may lead to a dampening of the HPA-axis controlled fight-or-flight response, further disabling the organism's ability to cope with chronic stress, as well as suppression of dopaminergic mechanisms in the NAcc, helping to sustain depressive behaviours.

1.5.5 Discrete stress-related impairments in reward processing

The hopelessness diathesis-stress model (Abramson et al., 2002) implicitly suggests that the stress-induced deficits in reward processing are specific to motivational or "wanting" aspects of the reward cycle. This supports the neurophysiological work discussed above, which points to decreased approach motivation in response to chronic stress (e.g. Lemos et al., 2012). However, this notion of specific approach-related stress-induced deficits in reward processing is not in-keeping with previously noted consummatory deficits in reward processing elicited by the CMS model, e.g.

impairments in liking sucrose-infused water (Moreau et al., 1992, 1993). A relatively nascent body of work may help to reconcile these findings by highlighting differences in stress-induced impairments in discrete aspects of the reward processing cycle, depending on the nature of the stressor. Work by Kumar et al. (2014) suggests that stress has dissociable effects on anticipatory versus consummatory aspects of reward processing and that these effects are linked to individual differences in perceived stress sensitivity (Kumar et al., 2015). In two studies using an fMRI paradigm, Kumar et al. (2014; 2015) induced stress in participants by incorporating a social evaluation component comprising negative feedback about task performance into a monetary incentive delay task (MID; Knutson, Westdorp, Kaiser & Hommer, 2000). Using this modified MID, Kumar et al. (2014) report acute stress-induced increased activation in the mesolimbic pathway, namely areas in the striatum, including the right caudate, and amygdala during the anticipation of rewards, accompanied by decreased activity in the striatum – specifically the left caudate and putamen - during the consummatory phase of reward processing. Building on this work, Kumar et al. (2015) report increased mPFC activity in response to reward feedback in participants with high perceived stress, undergoing a stress-induction paradigm. Similarly, participants with MDD revealed a positive correlation between their perception of the severity of an acute stressor and their reward-related activity in the mPFC. No such finding was evident among a group of healthy controls.

Similarly, Dillon, Holmes, Birk, Brooks, Lyons-Ruth and Pizzagalli (2009) report higher levels of anhedonia (based on the Mood and Anxiety Symptoms Questionnaire – MASQ; Watson, Clark, Weber, Assenheimer, Strauss & McCormick, 1995) and depression (assessed via the Beck Depression Inventory II – BDI-II; Beck, Steer & Brown, 1996) among individuals exposed to childhood adversity (relative to controls). Participants also underwent an fMRI scan whilst completing a version of the MID task. Relative to controls, participants who had experienced childhood adversity showed reduced anticipatory pleasure (they rated reward cues less positively) and showed an attenuated neural response to reward cures in the left globus pallidus. In contrast, there were no group differences in response to consummatory reward, no-incentive or loss cues, suggesting a specific impairment in stress-induced anticipatory reward processing. This study adds to prior experimental work by Pryce, Dettling, Spengler, Schnell and Feldon (2004), who observed increased anhedonic behaviour, specifically

decreased performance on a progressive ratio task, in marmosets in response to neglect-like manipulations in early life.

Taken together, this work tentatively suggests that stress differentially affects reward processing depending both on the phase of reward processing and characteristics of the individual, e.g. their stress sensitivity, as well as the chronicity of the stressor. For participants who are depressed or who have greater sensitivity to perceived stress, the mPFC may be recruited more strongly during reward processing, particularly in the reward consummation (relative to reward anticipation) phase. This is in-keeping with previously discussed literature suggesting that dopamine inhibits activity in the mPFC and that stress is linked to motivational impairments in reward processing. It should also be noted, however, that the studies discussed here are underpowered and thus further work is needed to confirm these findings.

1.5.6 Individual differences in stress sensitivity and the development of depression

Building on the relevance of individual differences in stress sensitivity in the development of depression, pre-clinical studies in healthy adults also points to a relationship between individual differences in the perception of stress and the experience of both increased anhedonia and decreased reward responsivity. Horan, Brown and Blanchard (2007) report higher levels of perceived stress among participants with increased social anhedonia (assessed via the Chapman Social Anhedonia Scale - CSAS; Eckbald, Chapman, Chapman & Mishlove, 1982). Despite a similar level of exposure to recent stressors, participants with high social anhedonia scores reported perceiving these stressors as more unpredictable, uncontrollable or otherwise overwhelming compared with less socially anhedonic participants.

Individual differences in the functioning of the mesolimbic dopaminergic pathway – particularly the reactivity of the ventral striatum (VS) play a role in mediating this stress-anhedonia link. Corral-Frías, Nikolova, Michalski, Baranger, Hariri and Bogdan (2015) report a structural equation model in which responsivity in the VS interacted with the experience of early life stress to predict higher symptoms of anhedonia. Building on this relationship, they report an association with other depressive symptoms via the mediating role of anhedonia. Taken together, these findings posit a

causal relationship, whereby early life stress and the mesolimbic dopamine system interact to give rise to anhedonic behaviours, which, in turn, lead to the development of depression.

In keeping with the hopelessness diathesis stress model and the neurobiological evidence suggesting chronic stress impairs approach motivation, a variety of behavioural paradigms suggest that stress blunts sensitivity to novel and future rewards. This decreased reward responsivity can be seen in a study conducted by Bogdan and Pizzagalli (2006). Participants' performance on a signal detection task (adapted from Pizzagalli, Jahn and O'Shea, 2005) was differentially reinforced to cultivate the development of a bias for one, preferentially rewarded, response. Participants completed the task twice: once under a no-stress condition, and a second time, during which they either completed the task under threat of shock or under a social evaluation condition (in which they were told they had an unfavourable performance ranking relative to past participants). Both social and threat of shock stressors impaired performance on the signal detection task (taken to indicate a reduction in reward responsiveness). Self-reported anhedonia (assessed via anhedonia subscales of the BDI-II and the MASQ) predicted stress-induced deficits in reward responsiveness, even after controlling for anxiety (provoked by the stressor). This experimental manipulation suggests a clear role for stressors – both social and physical - in cultivating reward processing deficits among individuals with higher trait anhedonia, pointing to anhedonia as a risk factor (or diathesis) in the development of stress-induced depression.

Building on this work, Pizzagalli, Bogdan, Ratner and Jahn (2007), link reductions in reward responsiveness (on the previously outlined signal detection task) with both higher levels of perceived stress and greater anhedonic symptoms. Across two studies, Pizzagalli et al. (2007) noted that participants who judged their lives to contain more unpredictable and uncontrollable stress (indexed by the Perceived Stress Scale (PSS); Cohen Kamarck & Mermelstein, 1983) were less able to modulate their behaviour as a function of reward (i.e. did not show a preferential reinforcement bias on the signal detection task), relative to participants with low PSS scores. Furthermore, participants with higher PPS scores reported significantly higher scores for depression (based on the BDI-II and MASQ) and anhedonia (based on the MASQ).

In summary, this work suggests a relationship between individual differences in the perception of stress and the existence of heightened anhedonia and depressive symptoms. The experience of acute stress seems to engender deficits in reward responsivity, which can be predicted by an individual's pre-existing levels of anhedonia and their sensitivity to stressors. In light of the work by Corral-Frías et al. (2015), it seems likely that sensitivity of dopaminergic mechanisms in the ventral striatum may mediate this stress-anhedonia link.

1.5.7 Frontal EEG asymmetry as a mediator between stress and anhedonia

Reflecting the possible stress-induced attenuation of reward processing and the role of the PFC in mediating these processes (e.g. Cuadra et al., 1999; Pizzagalli et al., 2007), a number of studies have attempted to examine the influence of stress on frontal EEG asymmetries. The role for relatively greater right (than left) frontal asymmetry as a diathesis for the development of stress-induced depression and / or a putative mediator or moderator of this relationship is fully discussed in Coan and Allen (2004). Briefly, this section will consider some work to support the relationship between relatively greater right cortical activity and the experience of stress and depression.

Reflecting Davidson's (1992) frontal EEG asymmetry diathesis model for depression (see section 1.7.1), Lopez-Duran, Nusslock, George and Kovacs (2012) report relatively greater right (than left) frontal cortical activation among 6 – 13- year old children at heightened risk of depression while watching emotion-eliciting video clips, in comparison to children at low risk of developing depression (risk was determined by the presence or absence of a first-degree relative with depression). Furthermore, in the high-risk group, greater relative left asymmetry (i.e. greater left cortical activation) moderated the relationship between the experience of stressful life events and internalising symptoms (e.g. anxiety, depression and behavioural withdrawal). Thus, suggesting a role for frontal EEG asymmetries as a moderating (or mediating) variable between stress and withdrawal / depressive tendencies.

An experimental analogue of this work, conducted by Pérez-Edgar, Kujawa, Nelson, Cole and Zapp (2013), examined the relationship between an acute stress induced

change in frontal EEG asymmetry and attention bias toward happy or angry faces in a group of healthy participants. Their findings suggested that those participants who responded to a social evaluation stressor (preparing and giving a speech) with increased right (relative to left) frontal cortical activation also showed an attention bias toward angry faces and away from happy faces. In contrast, participants who demonstrated increased left frontal activation in response to the stressor demonstrate no bias toward either face valence. These findings point to a link between relatively greater right cortical activity and increased threat vigilance, which is likely to be indicative of heightened stress perception.

Two recent studies provide further weight to the relationship between frontal EEG asymmetry and the experience of chronic stress. Hostinar et al. (2017) report an association between the experience of childhood maltreatment and greater right (relative to left) frontal EEG asymmetry in a large sample of 314 adults. These variables interacted to predict higher levels of physical inflammation (indexed by a composite measure of various cytokines – see section 1.10 for further discussion of the role of inflammation in the mechanistic pathway between stress and depression), so that relative right asymmetry predicted inflammation in participants who had experienced childhood abuse. Similarly, work by Tang, Miskovic, Lahat, Tanaka, MacMillan, Van Lieshout and Schmidt (2018) points to the potential for trait left (relative to right) frontal EEG asymmetry in moderating the relationship between childhood adversity and the subsequent development of psychopathologies, such as PTSD and depression. In a two-year longitudinal study of teenagers recruited from child protection services, Tang et al. (2018) observed stable right hemisphere dominance in approximately 60 per cent of participants and, conversely, left hemispheric asymmetry in 40 per cent of individuals. Despite experiencing similar levels of childhood adversity, those teenagers with left hemisphere dominance were less likely to have developed post-traumatic stress disorder (PTSD) and / or depression two years later.

Taken together, this work suggests that dominance of the right cerebral hemisphere may play a role in the development or maintenance of stress-induced psychopathologies, such as depression. Frontal EEG asymmetries seem to interact with the experience of stress, so that relatively greater right than left frontal EEG asymmetry (i.e. greater right cortical activity) may act as a mediator in the relationship between

stress and depression. In contrast, left hemispheric asymmetry may act as a protective factor, whereby it mitigates the severity of the relationship between stress and psychopathology, leaving the individual less likely to develop depression. It is less clear if the hopelessness diathesis stress model (Abramson et al., 2002) can be supported by this work. Work by Short, Lubach, Shirtcliff, Styner, Gilmore and Coe (2014) points to heightened responsivity to stress and a reduced willingness to approach novel stimuli in rhesus monkeys with high levels of cortisol. These behaviour patterns were not observed in monkeys with low cortisol levels, and were accompanied by attenuation of right frontal cortical regions, as well as reduced gray matter in the right frontal cortex. The reduced approach motivation demonstrated by these monkeys is likely to reflect a behavioural analogue of anhedonia and thus suggests a role for frontal EEG asymmetry in mediating the relationship between perceived stress and anhedonia.

1.5.8 The line bisection task: a proxy measure of EEG asymmetry

Line bisection tasks are used extensively in research and clinical practice to assess hemineglect. Visuospatial (or hemispatial) neglect is a neurological symptom resulting in a difficulty in attending, responding or orientating toward stimuli positioned in the visual field of the contralateral hemisphere (Jewell & McCourt, 2000). These impairments must not be attributable to sensory or motor impairment. Typically, hemineglect occurs due to damage to the brain's inferior parietal or temperoparietal lobe. However, impairments arising due to damage to frontal regions or the cingulate cortex have also been reported (Vallar, 1993). The line bisection task is commonly used with such populations as a behavioural index of hemisphericity, i.e. the relative dominance of the right or left hemisphere (Jewell & McCourt, 2000). The line bisection task typically takes the form of a pen and paper task, on which participants are presented with a series of straight, horizontal lines, which are staggered across the page, and are asked to indicate the midpoint on each line. A tendency to err to the left of the midpoint is taken to indicate relative primacy of the right (relative to left) visual field, which, in turn, suggests dominant activity in the contralateral hemisphere (in this instance the left hemisphere). Similarly, errors that are biased toward the right of the midpoint are taken to indicate greater activity in the right (relative to the left) cerebral hemisphere.

While the task was originally developed for use in clinical populations as an index of hemineglect, it has also been used as a proxy for frontal EEG asymmetry measures, i.e. to indicate situational or dispositional measurement of hemisphericity. As discussed throughout this thesis, the EEG asymmetry is frequently interpreted as an index of approach / withdrawal motivation, whereby relatively greater activity in the left (compared to the right) cerebral hemisphere is associated with greater approach motivation, while the converse is linked to increased withdrawal motivation (e.g. Sutton & Davison, 1997). Performance on the line bisection task has been linked to a variety of motivation-related phenomena, e.g. action-related emotions (Drake & Myers, 2006); Match.com profiles of sexually attractive people (Miller, Prokosch & Maner, 2012); and anxiety in relation to academic goals (McGregor, Nash, Mann & Phills, 2010). Performance on the line bisection task has also been linked directly to frontal EEG asymmetry in a sample of 29 right-handed, healthy females, by Nash, McGregor and Inzlicht (2010). In this study, participants completed the line bisection task and underwent a resting state EEG recording. Leftward bias on the line bisection task (thought to indicate relatively greater left cortical activation), was correlated with relatively greater left (than right) cortical activity in the EEG asymmetry index. This correlation was significant only for electrode sites F7 and F8 (two of the sites most commonly used in the calculation of the EEG asymmetry index). Nash, McGregor and Inzlicht (2010) argue that this relationship supports the use of the line bisection task as a proxy measure of dispositional EEG frontal asymmetry.

In a second sample of 29 participants, Nash, McGregor and Inzlicht (2010) demonstrated that performance on the line bisection task is sensitive to the same situational aspects of the environment as the frontal EEG asymmetry. Specifically, they conceptually replicated an earlier study, in which individuals with high self-esteem demonstrated increased approach motivation (quantized by a pre-post increase in left – relative to right - EEG asymmetry) in response to a challenging stimulus (McGregor, Nash & Inzlicht, 2009). In study 2 (of Nash, McGregor & Inzlicht, 2010), participants were similarly challenged (i.e. they were asked to describe a recent academic dilemma they had experienced). Relative to baseline, participants with high self-esteem showed increased rightward errors on the line bisection task (indicative of relatively greater left – than right – EEG asymmetry).

To our knowledge, only one prior study has considered the line bisection task as a proxy for frontal EEG asymmetry in relation to stress (Naylor, Byrne & Wallace, 2015). This study invoked acute stress through a combination of social evaluation and performance pressure on participants' engagement in a motor skill task. Similar to the present study, the line bisection task was implemented as a proxy for EEG asymmetry indexed trait motivation. Participants with higher trait approach tendencies (assess by the BIS / BAS Drive subscale) responded to the performance pressure with a rightward bias on the line bisection task (indicative of greater left frontal asymmetry) pre-task, relative to their low trait approach peers. However, after failing on the task, high trait approach participants demonstrated a reversal of their line bisection performance, thus suggesting relatively greater right cortical activation in response to failure. This effect was not observed in low trait approach participants.

Unpublished work from our own lab, recently presented by Stavrou, Cooper and Pickering (2018) lends support to the relationship between approach motivation and rightward bias on the line bisection task. In this study, an increase in rightward bias on an electronic version of the line bisection task (reflective of relatively greater left hemispheric activity) was observed (relative to baseline) after watching an appetitively-motivational video. No such increase was observed in a control group, who watched an informational (i.e. non-motivational) video. Taken together, the results of these studies suggest that the line bisection task may be a useful and appropriate proxy measure for frontal EEG asymmetry, particularly when taken as an indicator of approach / withdrawal tendencies.

1.5.9 Rationale

The research discussed thus far points to stress-induced alterations in reward processing that interact with mesocortical dopaminergic mechanisms to produce anhedonic behaviour (Cabib & Puglisi-Allegra, 2012). Such behaviour is characterised by a reduction in anticipatory pleasure, but a relatively preserved level of consummatory pleasure (e.g. Pryce et al., 2004). The nature of the stressor is a crucial factor in this process. Specifically, chronic stress, perceived by the individual to be inescapable or uncontrollable, rather than acute or avoidable stressors, elicit these reward processing deficits (Pizzagalli, 2014). Building on this observation, individual differences in stress

sensitivity are of primary interest, as individuals more inclined to perceive stressors as inescapable or overwhelming are more likely to develop anhedonic behaviours, which may specifically relate to anticipatory deficits in interpersonal domains (e.g. Horan, Brown and Blanchard, 2007). Based on the small body of prior work examining the role of frontal EEG asymmetries in relation to early life and naturalistic stressors, it seems reasonable to assume that frontal EEG asymmetry (and its proxy used in this chapter – performance on the line bisection task) would mediate the relationship between perceived stress and anhedonia. We anticipate that it would do so in those instances where stress predicts anhedonia, i.e. for anticipatory rather than consummatory deficits (Lopez-Duran et al., 2012) and in interpersonal / social domains (Horan, Brown & Blanchard, 2007; Kumar et al., 2014; 2015). Given prior reports that the experience and perception of stress was differentially related to anticipatory versus consummatory phases of reward processing (Kumar et al., 2014; 2015), it was expected that perceived stress would predict anticipatory, but not consummatory anhedonia scores on the TEPS, and that performance on the line bisection task would differentially predict anticipatory versus consummatory anhedonia.

1.5.10 Hypotheses

The present study assessed fourteen hypotheses in an attempt to better characterise the relationships between discrete aspects of anhedonia, stress and a proxy measure of cerebral asymmetry. First, we aimed to investigate whether stress would predict anhedonia in each of the four areas assessed by the GAME: Interpersonal, Emotional, Sensory and Drive / novelty seeking. Seven hypotheses were presented in relation to the GAME (H1 – H7). It was predicted that greater perceived stress would predict higher levels of anhedonia in interpersonal (H1) and emotional (H2) domains as well as on the drive (H3) subscale, but not on the sensory subscale (H4), due to the primarily consummatory nature of the items on the sensory pleasure subscale. It was further predicted that performance on the line bisection task would partially mediate the relationship between stress and anhedonia for the interpersonal (H5), emotional (H6) and drive (H7) subscales. Specifically, it was expected that greater right hemisphere bias (indicated by an average leftward error on the line bisection task) would be associated with higher levels of anhedonia.

A further three hypotheses are presented in relation to the TEPS: Perceived stress is expected to predict anticipatory pleasure (TEPS ANT; H8), but not consummatory pleasure (TEPS CON; H9). Performance on the line bisection task is expected to partially mediate the relationship between perceived stress and the TEPS ANT (H10).

Finally, in an attempt to further validate the GAME, we expected that scores on three GAME sub-scales (i.e. interpersonal, emotional and novelty-seeking domains) would be related to levels of depression on the BDI-II. Specifically, higher levels of depression would be associated with higher levels of anhedonia on the interpersonal (H11), emotional (H12) and drive (H13) subscales, but not on the sensory pleasure subscale (H14), given reports that anhedonic depression is associated primarily with deficits in anticipatory pleasure, but relatively preserved consummatory pleasure (e.g. Sherdell, Waugh & Gotlib, 2012).

5.2 Method

5.2.1 Participants

328 (178 female; *M* age = 34.64 years, *SD* = 9.9 years) right-handed participants were recruited via the website Prolific Academic. 34 participants were excluded due to incomplete data (primarily due to their performance on the line bisection task, i.e. either a failure to complete a sufficient number of trials or due to indicating the mid-point as being within 10 per cent of either end point – see section 5.2.2.1 for further details). The final *N* = 294 participants (150 female; *M* age = 35.04, *SD* = 10.37 years; range 18 – 65 years). Participants were paid £1.67 for completing the survey (approximately £5 for one hour of participation). Participants were excluded if they met any of the following criteria: left-handed; self-reported previous history of psychiatric illness; non-native English speaker; currently enrolled as a student; had previously participated in a study using this questionnaire (see chapter four for more information). This study received ethical approval from the Ethics Committee of the Psychology Department at Goldsmiths, University of London.

5.2.2 Materials

This study comprised four questionnaire measures and a behavioural task thought to indicate frontal EEG asymmetry. All measures were administered online via the survey website Qualtrics.

5.2.2.1 The line bisection task

The line bisection task is a behavioural task taken to indicate relative cerebral hemisphericity (Jewell & McCourt, 2000). This task is typically administered via pen and paper methods and is widely used to assess patients experiencing neurological symptoms such as visual neglect. On this task, participants are asked to indicate the middle of a series of straight, horizontal lines. Errors in estimating the middle of the line - toward either the right or the left of the midpoint – are taken to indicate the relative dominance of the left or right hemisphere (and related neural activity) respectively.

In the current study, the line bisection task was administered online, modelled after the method proposed by Stavrou, Cooper and Pickering (2018). Participants were presented with a series of 30 lines on sequential screens (so that they could not use the previous line as a reference). Each line was horizontal, and appeared either in the middle of the screen or staggered slightly left or right of the middle of the screen. Each line also had a blue circle, which was randomly placed at either the left or right extreme of the line (see Figure 5.1). Participants were required to indicate the midpoint of the line by clicking the centre of the line with the mouse or cursor. Participants were given the following instructions before starting the task:

You will now be shown a series of scales in the shape of a thin bar. Your task is to line up your cursor to where you think ***the centre of the bar*** *is and* ***click*** *(you may have to double click). Once you click on where you feel the midpoint is, the round pointer will appear in that spot and* ***mark where you have bisected the bar****. You then click next (--->) to go on to the next trial.*
You must do this as fast as possible, without thinking too much, and without turning back.

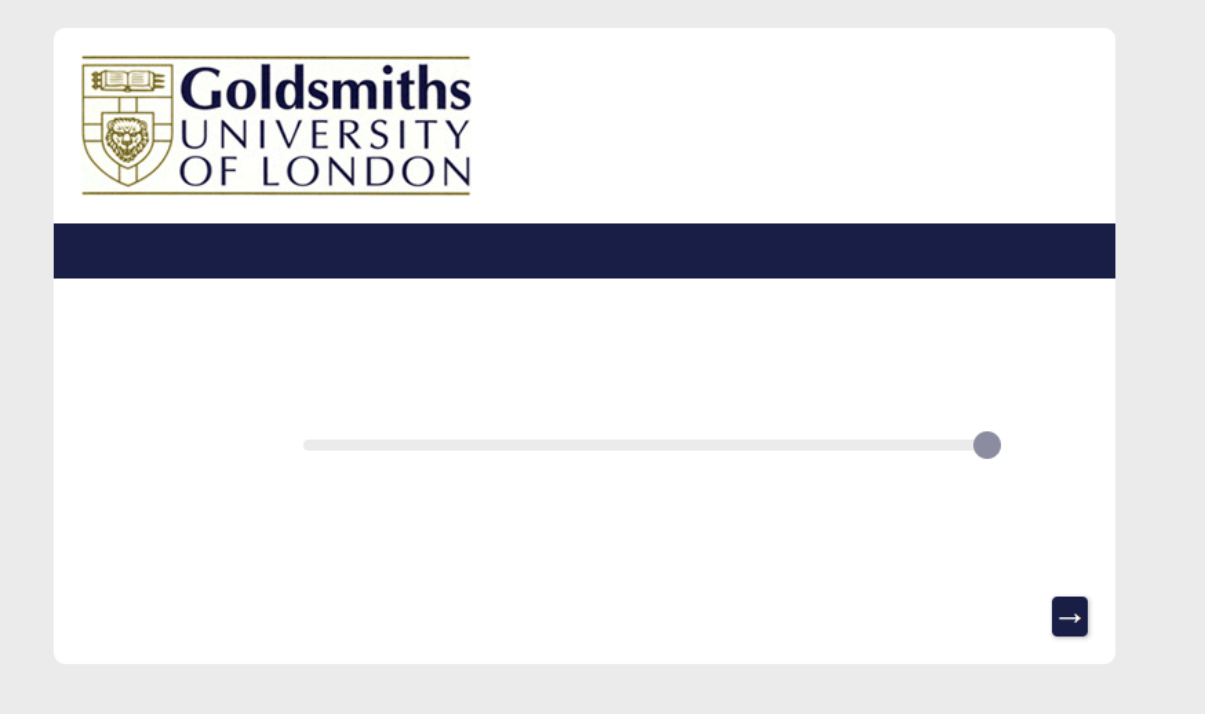

Figure 5.1 An example of the line bisection task used in the present study. Participants were presented with this screen and asked to indicate the midpoint of the line by clicking once. The blue dot then moved to their chosen midpoint and participants were asked to continue to the next trial.

An average value was computed for each participant, based on their overall line bisection task performance. To do this, data were first screened to ensure participants had made a reasonable attempt at bisecting the line. The line was scored from 0 to 100, so that 0 represented the leftmost end of the line and 100 represented the rightmost end of the line. Thus, the true midpoint of the line was the value 50. Using this metric, participants' left (or right) bias on the task was calculated so that right-ward scores (i.e. greater than 50) had a positive value (and indicated left hemispheric activity) and left-ward scores (i.e. less than 50) had a negative score (and indicated right hemispheric activity). Lines that were bisected within 10 points of either extreme on an individual line (i.e. between 0-10 or between 90-100) were deemed invalid attempts and were removed from the analysis. Participants with fewer than 10 valid attempts on the line bisection task across the 30 trials were excluded from the analysis. On average, the included participants completed 29.46 line bisections (*SD* = 2.46) with the median number of completed tasks = 30. Once this data screening was complete, all valid attempts at the line bisection task were averaged and 50 (i.e. the true midpoint) was

subtracted from this average to provide a small positively or negatively valenced number, taken to reflect frontal asymmetry toward the right or left cerebral hemisphere respectively. Reliability of the line bisection task was excellent in the present study (Cronbach's α = .88; MacDonald's Omega ω_T = 0.9)

5.2.2.2 Psychometric measures

5.2.2.2.1 The Goldsmiths Anhedonia Measure (GAME)

A revised version of the GAME was presented to participants, in line with the recommendations from the confirmatory analysis presented in chapter 4. This revised version of the GAME comprised 40 items (see table 5.1) ranging over four subscales: Interpersonal anhedonia (IA; 14 items); Negative Emotionality (NE; 12 items); Sensory Pleasure (SP; 8 items); and Drive (D; 6 items). As in previous versions of the questionnaire, items were presented to participants alongside a 1 – 5 Likert scale, where 1 = very false for me and 5 = very true for me. Participants were given the following, modified instructions:

You are about to read a number of statements that describe people's behaviours, thoughts or feelings. Please read each statement carefully. Use the rating scale to indicate how accurately each statement describes you. Describe yourself as you generally are now, not as you wish to be in the future. Describe yourself as you honestly see yourself. So that you can describe yourself in an honest manner, your responses will be anonymous and kept in absolute confidence.

These instructions were modified (compared to those used in chapter 4), in order to make the instructions more clear for participants. Specifically, we removed the age and sex comparison, as this is not a standard instruction.

Individual scores were calculated for each subscale, scored to indicate anhedonia in each domain (i.e. positively valanced statements such as "*The smell of freshly cut grass is enjoyable to me*" were reverse scored). The reliability estimates of the GAME varied widely in the present study. Specifically, the IA and NE subscales showed

excellent reliability (IA α = .86, *n*items = 14; NE α = .83, *n*items = 12), while reliability for Drive was weaker (α = .59, *n*items = 6) and very poor for SP (α = .32, *n*items = 8). MacDonald's omega indicated strong reliability for the four-factor model (ω_T = 0.89).

Table 5.1: The 40-item Goldsmiths Anhedonia Measure. Subscales and their corresponding statements are indicated in order of presentation.

Item number	Subscale	Statement
1	IA	I have no interest in having strong relationships with other people
2	NE	I often feel blue
3	SP	I have often enjoyed the feeling of silk, velvet or fur
4	D	I crave excitement and new sensations
5	IA	Having close friends is not as important as many people say
6	NE	I am disappointed with myself
7	SP	I have been fascinated with the dancing of flames in a fireplace
8	D	I want to be the very best
9	IA	I attach very little importance to having close friends
10	NE	I have a low opinion of myself
11	SP	On seeing a soft, thick carpet, I have sometimes had the impulse to take off my shoes and walk barefoot on it
12	D	I get so excited the night before a fun event I can hardly sleep
13	IA	Making new friends isn't worth the energy it takes
14	NE	I feel that my life lacks direction
15	SP	The smell of freshly cut grass is enjoyable to me
16	IA	I'm much too independent to really get involved with other people
17	NE	I am critical of myself for my weaknesses and mistakes
18	SP	When I have seen a statue I have had the urge to reach out and touch it
19	D	How I dress is important to me
20	IA	I am disinterested in other people
21	NE	I don't enjoy the things I used to
22	SP	I really enjoy the feeling of a good yawn
23	D	I often act on the spur of the moment
24	IA	Other people's daily activities and opinions are of no interest to me
25	NE	I find it difficult to get down to work
26	SP	I have never had the desire to take my shoes off and walk through a puddle barefoot
27	D	When I'm on my way to an amusement park I can hardly wait to ride the rollercoasters
28	IA	There are few things more tiring than to have a long personal conversation with someone
29	NE	It takes extra effort to get started at doing something

30	SP	I have sometimes danced by myself just to feel my body move with the music
31	IA	I have often felt uncomfortable when my friends reach out to touch me
32	NE	I put off making decisions
33	IA	I don't really look forward to family get-togethers or gatherings
34	NE	I don't sleep well
35	IA	When I am alone I often resent people telephoning or texting me or knocking on my door
36	NE	I get annoyed or irritated easily
37	IA	I never really had close friends in high school
38	IA	My relationships with other people never get very intense
39	NE	I worry about my health, including physical problems such as aches and pains or upset stomach and constipation
40	IA	I prefer watching television to going out with other people

Note: IA = Interpersonal Anhedonia; NE = Negative Emotionality; SP = Sensory Pleasure; D = Drive.

5.2.2.2.2 The Perceived Stress Scale (PSS)

The perceived stress scale (PSS: Cohen, Kamarck & Mermelstein, 1983) is a well validated measure of perceived stress. The 10-item scale aims to assess the extent to which individuals perceive their lives to be stressful, based on how frequently they have experienced unpredictable, uncontrolled or anxiety-provoking events in the past month, e.g. "*In the last month, how often have you been upset because of something that happened unexpectedly?*" The response scale ranges from 0 to 4, where 0 = *Never* and 4 = *Very often*. Reliability for the PSS was excellent in the present sample (Cronbach's α = .86; *n*items = 10).

5.2.2.2.3 The Temporal Experience of Pleasure Scale (TEPS)

The TEPS (Gard, Germans Gard, Kring & John, 2006) has been fully described elsewhere (see chapter 2). Briefly, this 18-item scale assesses the experience of pleasure in two domains: anticipatory and consummatory. Each sub-scale is scored on a Likert scale from 1 (*"very false for me"*) to 6 (*"very true for me"*). Items for each sub-scale are summed and the sub-scales can be combined to give a total score indicative of overall trait hedonic tone. For the current sample, Cronbach's alpha suggested high reliability (α = .74; *n*items = 10) for the anticipatory subscale, but was slightly below

the often-cited 0.7 threshold of acceptability (α = .63; *n*items = 8) for the consummatory subscale. MacDonald's Omega also indicated strong reliability for the two-factor model (ω_T = 0.83).

5.2.2.2.4 The Beck Depression Inventory II (BDI-II)

The BDI-II (Beck, Brown & Steer, 1996) has also been fully outlined in Chapter 2. Briefly, this is a 21-item self-report questionnaire used to assess depression severity in both clinical and healthy samples. Questions are answered by selecting one of four options to indicate symptom severity, ranging from not present (0) to severe (3). The measure is sensitive to a range of symptoms of depression, including anhedonia, self-criticism and recent changes in appetite and sleep. The current sample had excellent reliability; Cronbach's α = .896 (for 21 items). The maximum possible score for the BDI-II is 63 and the authors provide the following suggested cut-off scores: 0-13: minimal depression; 14-19: mild depression; 20-28: moderate depression; 29-63: severe depression. minimal depression on average (see table 5.2). Based on these cut off scores, in the current sample, 64.3 per cent (*N* = 189) showed minimal depression; 15.3 per cent (*N* = 45) showed mild depression; and 14.6 per cent (*N* = 43) showed moderate depression; and 5.8 per cent (*N* = 17) showed severe depression.

5.2.3 Procedure

Participants meeting the eligibility criteria (see section 5.2.1) were invited to participate in the study via Prolific. Upon expressing interest in the study, participants were taken via an external link to the Qualtrics site where the study was hosted. Participants were presented with an information sheet, which outlined the requirements of the study, and a consent form. Upon consenting to participate in the study, participants completed the GAME, line bisection task, PSS, TEPS and BDI-II. They were then debriefed and given a code with which they could claim payment for their participation via Prolific.

5.2.4 Statistical analyses

In order to compare the four-factor structure for the revised 40-item GAME structure to the original 50-item structure, two Confirmatory Factor Analyses was carried out using the Psych package in R. Model fit was assessed using the Root Mean Square

Error of Approximation (RMSEA) and the Comparative Fit Index (CFI), in line with recommendations by Kline (2011). As noted in Chapter 4, the RMSEA assesses whether the specified model is a reasonable approximation of the data, with values closer to 0.0 indicative of better fit (Beaujean, 2014). Debate exists over the utility of cut-off scores to enable qualitative judgement of goodness of fit (see Lai & Green, 2016), however, the most widely used cut-offs for RMSEA suggest that values less than 0.05 (Browne & Cudeck, 1992) or 0.06 (Hu & Bentler, 1999) are indicative of a "good" fit, while values between .05 and .10 suggest "acceptable" fit (Browne & Cudeck, 1992). The CFI provides an index of the difference of fit between the hypothesised model and an independence model, which specifies zero correlation between all of the observed variables). A CFI of 0.9 is usually interpreted as an acceptable fit, with values above 0.95 indicative of a good fit (Hu & Bentler, 1999).

In order to provide further validation of the GAME, correlational analyses were run between individual subscales of the 40-item GAME and the BDI-II. These were run using SPSS, version 24 for Mac.

To test the main hypotheses, i.e. that performance on the line bisection task would mediate the relationship between perceived stress and discrete subscales of anhedonia, the PROCESS Macro for SPSS was used (Hayes, 2018) to conduct a series of mediation analyses.

5.3 Results

5.3.1 Descriptive statistics

Means and standard deviations for all variables are presented in table 5.2.
Correlational relationships between the variables (corrected for multiple comparisons) are depicted for descriptive purposes in table 5.3.

Table 5.2: Means and standard deviations for all 10 variables in this study

	Mean	Standard Deviation
GAME D (6 items)	13.38	3.22
GAME IA (14 items)	35.44	10.22
GAME NE (12 items)	34.93	8.27
GAME SP (8 items)	12.89	4.16
Line Bisection (30 items)	.251	2.12
PSS (10 items)	17.75	7.02
BDI-II (21 items)	12.29	9.11
TEPS Total (18 items)	78.14	11.87
TEPS ANT (10 items)	41.42	7.99
TEPS CON (8 items)	36.73	5.94

Note: For the GAME: IA = Interpersonal Anhedonia; NE = Negative Emotionality; SP = Sensory Pleasure; D = Drive; PSS = Perceived Stress Scale; BDI-II = Beck Depression Inventory II; TEPS = Temporal Experience of Pleasure Scale (ANT = Anticipatory – and CON = Consummatory -subscales).

The means and standard deviations for the GAME in this sample broadly reflect those observed in previous samples using the GAME (see Table 5.3).

Table 5.3: Sample characteristics, mean score, standard deviation for a single item of each subscale of the GAME and reliability indices for all three samples from chapters 4 and 5

	No. of items per subscale	Sample 1 Study 1, Chapter 4	α	Sample 2 Study 2, Chapter 4	α	No. of items per subscale	Sample 3 Chapter 5	α
N participants		523		311			294	
Age (in years)		39.94 (11.67)		40.07 (11.48)			35.04 (10.37)	
ω_T		0.93		0.90			0.89	
GAME IA*	15	2.63 (0.78)	.902	2.57 (0.74)	.889	14	2.53 (0.73)	.86
GAME NE*	14	2.98 (0.71)	.846	2.82 (0.65)	.822	12	2.91 (0.69)	.83
GAME SP*	14	2.96 (0.48)	.691	2.38 (0.5)	.699	8	1.61 (0.52)	.32
GAME Drive*	8	3.14 (0.85)	.689	2.96 (0.53)	.694	6	2.23 (0.54)	.59

*Note: Mean score (and standard deviation) per item; ω_T = MacDonald's omega; α = Cronbach's alpha; IA = Interpersonal Anhedonia; NE = Negative Emotionality; SP = Sensory Pleasure.

5.3.2 Confirmatory Factor Analysis

The fit and modification indices yielded by the original CFA of the GAME (see study 2, chapter 4) suggested some revisions to the structure of the questionnaire to improve the model fit. Thus, the original 50-item GAME was refined to a 40-item measure (see chapter 4 for more information). The 40 item GAME is presented in Table 5.1.

The fit indices for the present study showed a slight improvement relative to the CFA sample (Study 2, Chapter 4). The CFA for the original 50-item GAME yielded the following fit indices: $X^2 = 2250$, $p < 0.001$; CFI = 0.701; RMSEA = 0.0561 [90% CI: 0.0525, 0.0596]. The fit indices for the revised (40-item) GAME provided a similar, albeit slightly better, fit: $X^2 = 1940$, $p < 0.001$; CFI = 0.79; RMSEA = 0.056 [90% CI: 0.052 – 0.061]. Similar to the CFA in Chapter 4, these fit indices provided mixed, but tentative support for a four-factor structure. The significance of the Chi square test is to be expected, given the relatively large sample size. The RMSEA for both the 50-item and 40-item GAME suggest adequate fit, which is very similar to that observed with the 50-item GAME in study 2, Chapter 4 (where RMSEA = 0.054, 90% CI [0.051, 0.058]). Ultimately, we decided to adopt the 40-item GAME for the rest of the analyses as this CFI (0.79) better approximates that observed in the original CFA sample (where CFI = 0.79) and this value is higher than that yielded by the 50-item GAME in the present sample (0.70), suggesting that the 40-item version is a slightly better fit. It should also be noted that the CFI value for the 40-item GAME is still lower than the threshold for adequate fit (CFI = 0.9) specified by Hu and Bentler (1999). The likely explanation for this was discussed in chapter 4.

5.3.2 Main analyses

Note that each set of hypotheses, as laid out below is considered a statistical family and a correction to preserve the family-wise error rate, in light of multiple comparisons, is noted.

Hypotheses 1 - 3

Hypothesis one to three (H1 - H3) predicted that higher perceived stress scores would predict higher levels of anhedonia in interpersonal (H1) and emotional (H2) domains as well as on the drive (H3) subscale of the GAME.

H1 was supported; perceived stress scores on the PSS predicted interpersonal anhedonia (IA) ($\beta = .123$, $p = .035$). However, this relationship would not survive correction for multiple comparisons ($\alpha = 0.05 / 3 = 0.017$). H2 was supported; higher PSS scores significantly predicted higher NE scores ($\beta = .63$, $p < 0.001$). In contrast, H3 was not supported; PSS scores did not predict performance on the Drive subscale of the GAME ($\beta = .078$, $p = .183$).

Hypothesis 4

Owing to the largely consummatory nature of the items on this subscale, stress was not expected to predict scores on the sensory perception (SP) subscale of the GAME. This null hypothesis was not rejected ($\beta = .028$, $p = .634$). To establish the strength of the evidence in support of the null hypothesis, a Bayesian correlational analysis was carried out using JASP (JASP Team, 2018). The analysis yielded a Bayesian correlation of $r = .03$ with a Bayes factor of $B_{01} = 12.23$ in favour of the null hypothesis, suggesting that the null hypothesis is approximately 12 times more strongly supported by the data compared with the alternative hypothesis (i.e. that perceived stress and sensory anhedonia are related). This is conventionally taken to indicate "strong evidence" in support of the null hypothesis (Lee & Wagenmakers, 2013).

Hypotheses 5 - 7

It was further predicted that performance on the line bisection task would partially mediate the relationship between stress and anhedonia for the interpersonal (H5), emotional (H6) and drive (H7) subscales. Specifically, it was expected that greater right hemisphere bias (indicated by an average leftward error on the line bisection task)

would be associated with higher levels of anhedonia. The mediation model is specified in Figure 5.2.

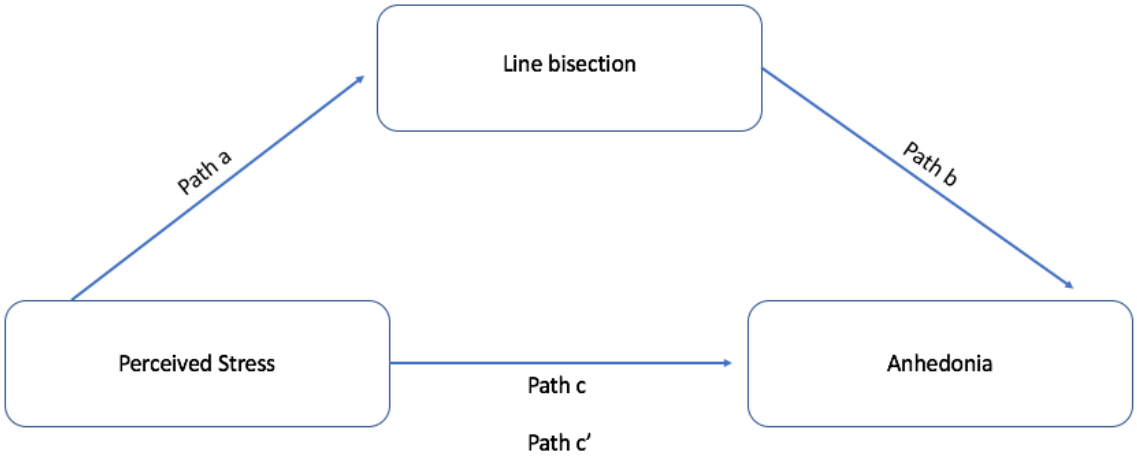

Figure 5.2: This figure depicts a generic version of the mediation models tested in hypotheses 5, 6, 7 and 9. Perceived Stress = scores on the PSS; Line bisection = average leftward bias (indicative of relative right cerebral asymmetry); Anhedonia = greater levels of anhedonia, as assessed by the GAME subscales; interpersonal anhedonia (H5); negative emotionality (H6); drive (H7); and the anticipatory pleasure subscale of the TEPS (H9).

Preliminary correlational analyses were carried out to test the assumptions of the mediation model (see Table 5.4). For H5, i.e. that performance on the line bisection task would partially mediate the relationship between stress and anhedonia for the interpersonal, the correlation between perceived stress and performance on the line bisection task (path a) was non-significant (r = .034, p = .557, B_{10} = .09)[1]. Similarly, path b, which tested the correlation between scores on the line bisection task and interpersonal anhedonia was non-significant (r = -.01, p = .85, B_{10} = .07). This suggests

[1] A Bayes factor was calculated to provide an estimate of the strength of the support for the null hypothesis. B_{10} represents the Bayes factor for the alternative hypothesis (H1), relative to the null hypothesis (H0). Values lower than 1 indicate relatively greater support for the null hypothesis and B_{01} (i.e. the Bayes factor for the null hypothesis) = $^1/B_{10}$. Thus, a B_{10} = 0.09 would imply a B_{01} of approximately 11, i.e. strong support in favour of the null hypothesis.

"strong evidence" in support of the null (relative to the alternative) hypothesis. Finally, the relationship between PSS scores and interpersonal anhedonia (path c) was significant (r = .123, p = .035, B_{10} = .68). However, this relationship did not survive correction for multiple comparisons (α = 0.05 / 10 = 0.005, i.e. p adjusted for a total of 10 tests: 3 mediation analyses each with 2 unique correlations per mediation model (i.e. 6 correlations in total), plus the correlation between the PSS scores and line bisection task), plus 3 tests of the mediation effect (even if these were not required). As the assumptions for the mediation analysis were not met, no mediation test was performed.

H6 predicted that performance on the line bisection task would partially mediate the relationship between stress and anhedonia for the emotional subscale of the GAME. As noted previously, path a, which tested the relationship between PSS scores and performance on the line bisection task was not significant (r = .034, p = .557, B_{10} = .09). Similarly, path b, which tested the correlation between scores on the line bisection task and the negative emotionality subscale of the GAME, was non-significant (r = -.01, p = .914, B_{10} = .07), suggesting strong support for the null hypothesis, relative to the alternative hypothesis. Finally, the relationship between PSS scores and negative emotionality (path c) was significant (r = .630, p < 0.001, $B_{10} = 5.78^{E+30}$), indicating "decisive support" for the null (relative to the alternative) hypothesis. Thus, higher perceived stress significantly predicted higher levels of anhedonia on the negative emotionality subscale of the GAME. As the assumptions for the mediation analysis were not met, no mediation test was performed.

H7 predicted that performance on the line bisection task would partially mediate the relationship between stress and anhedonia for the drive subscale of the GAME. As noted previously, path a, which tested the relationship between PSS scores and performance on the line bisection task was not significant (r = .034, p = .557, B_{10} = .09). Similarly, path b, which tested the correlation between scores on the line bisection task and the drive subscale of the GAME, was non-significant (r = -.05, p = .394, B_{10} = .11). This Bayes factor falls slightly below the conventional threshold (B_{01}>10) indicating strong support for the null (relative to the alternative) hypothesis. Finally, the relationship between PSS scores and drive (path c) was not significant (r = .078, p = .183, B_{10} = .18), indicative of "substantial support" for the null (relative to the

alternative) hypothesis. As the assumptions for the mediation analysis were not met, no mediation test was performed.

Hypotheses 8 - 10

A further three hypotheses were presented in relation to the TEPS: Perceived stress was expected to predict anticipatory pleasure (H8), but not consummatory pleasure (H9), on the TEPS subscales. Performance on the line bisection task is expected to mediate the relationship between perceived stress and the TEPS ANT (H10). Significance is assessed at $\alpha = 0.05 / 5 = 0.01$ (adjusted for multiple comparisons; 5 significance tests are required to assess this family of 3 hypotheses).

Two regression analyses were carried out to assess the relationship between perceived stress and scores on the TEPS (H8 and 9). Scores on the PSS significantly predicted scores on the TEPS ANT ($\beta = -.154$, $p = .008$). This suggests that higher levels of perceived stress are related to lower levels of anticipatory pleasure on the TEPS. The second regression tested whether PSS scores would predict consummatory pleasure (TEPS CON). This relationship was non-significant ($\beta = -.036$, $p = .536$).

To establish the strength of the evidence in support of H9, i.e. the null hypothesis that perceived stress did not predict the level of consummatory pleasure, a Bayesian correlational analysis was carried out. The analysis yielded a Bayesian correlation of $r = -.04$ with a Bayes factor of $B_{01} = 11.31$ in favour of the null hypothesis, suggesting that the null hypothesis is approximately 11 times more strongly supported by the data compared to the alternative hypothesis (i.e. that perceived stress and consummatory pleasure are related). This indicates strong evidence in support of the null hypothesis (Lee & Wagenmakers, 2013).

H10 predicted that performance on the line bisection task would partially mediate the relationship between stress and anhedonia for the anticipatory subscale of the TEPS. Path a, which tested the relationship between PSS scores and performance on the line bisection task was not significant ($r = .034$, $p = .557$, $B_{10} = .09$), providing strong evidence in support of the null hypothesis. In contrast, the correlation for path b, i.e.

between scores on the line bisection task and the TEPS ANT, was significant (r = .145, p = .013, B_{10} = 1.6), suggesting anecdotal support (sometimes this level of support is also described as "barely worth mentioning") for the alternative (relative to the null) hypothesis (Wagenmakers et al., 2018). Finally, the relationship between PSS scores and scores on the TEPS ANT (path c) was significant (r = -.154, p = .008, B_{10} = 2.4), providing anecdotal evidence for the alternative (relative to the null) hypothesis (Wagenmakers et al., 2018). As the assumptions for the mediation analysis were not met (i.e. the correlation for path a was non-significant), no mediation test was performed.

Hypotheses 11 – 13

In an attempt to further validate the GAME, scores on three GAME sub-scales (i.e. interpersonal, emotional and novelty seeking domains) were expected to significantly correlate with levels of depression on the BDI-II. Specifically, higher levels of depression would be associated with higher levels of anhedonia on the interpersonal (H11), emotional (H12) and drive (H13) subscales, but not on the sensory pleasure subscale (H14). Significance, adjusted for multiple comparisons, was assessed at α = 0.05 / 3 = 0.017.

H11 and 12 were supported. A strong significant correlation emerged between negative emotionality and depression, whereby higher levels of depression were related to higher scores on the GAME NE (r = .678, p < 0.001, B_{10} = 4.447e+37), suggesting decisive evidence in support of the alternative (relative to the null) hypothesis. A weaker but still significant relationship was observed between higher BDI-II scores and greater interpersonal anhedonia (r = .207, p < 0.001, B_{10} = 40.85), again indicating decisive support for the alternative (relative to the null) hypothesis. H13 revealed a very weak, but significant relationship between BDI-II scores and scores on the drive subscale of the GAME (r = .067, p = .25, B_{01} = 7.08), indicating substantial support for the null hypothesis.

Hypothesis 14

Finally, H14, that the sensory pleasure subscale of the GAME would not be significantly correlated with BDI-II scores was tested using a Bayesian correlational analysis. The analysis yielded a Bayesian correlation of $r = .07$ with a Bayes factor of $B_{01} = 6.79$ in favour of the null hypothesis, suggesting that the null hypothesis predicts the data approximately 7 times better than the alternative hypothesis (i.e. that perceived stress and consummatory pleasure are related). This indicates moderate evidence (a.k.a "substantial support") for the null hypothesis (Lee & Wagenmakers, 2013).

Table 5.4 presents correlational relationships between all 9 variables in the present study. Correlations are corrected for multiple comparisons so that α (0.05 / 36) = 0.0014.

Table 5.4: Correlations between all variables

	1	2	3	4	5	6	7	8	9
1. GAME D									
r	1								
p									
2. GAME IA									
r	.336*	1							
p	.000								
3. GAME NE									
r	.164*	.307*	1						
p	.000	.000							
4. GAME SP									
r	.275*	.186	.056	1					
p	.000	.001	.337						
5. Line Bisection					1				
r	-.05	-.01	-.01	-.05					
p	.394	.850	.914	.406					
6. PSS									
r	.078	.123	.630*	.028	.034	1			
p	.183	.035	.000	.634	.557				
7. BDI-II									
r	.067	.207*	.678*	.070	-.13	.675*	1		
p	.249	.000	.000	.235	.032	.000			
8. TEPS ANT									
r	-.48*	-.36*	-.29*	-.24*	.145	-.154	-.23*	1	
p	.000	.000	.000	.000	.013	.008	.000		
9. TEPS CON									
r	-.22*	-.28*	-.17	-.49*	.071	-.036	-.16	.439*	1
p	.000	.000	.003	.000	.227	.563	.005	.000	

*$p < 0.0014$, adjusted for multiple comparisons ($\alpha = 0.05 / 36$).

5.4 Discussion

This study sought to achieve three core aims. First, we hoped to establish a relationship between individual differences in perceived stress and the prediction of anhedonic deficits (H1 – 4 and H8 – 9). Specifically, we expected perceived stress to predict anhedonia in social, emotional and drive / novelty seeking domains, as measured by the GAME (Hypotheses 1 – 3). In contrast, no significant relationship was expected between stress and physical / sensory anhedonia measured by the GAME (H4). Building on these hypotheses, we sought to test whether perceived stress would predictive anticipatory pleasure (H8), but not consummatory pleasure (H9), as

measured by the TEPS (Gard et al., 2006). Second, we hoped to establish a role for cerebral asymmetry (indexed by performance on a line bisection task) in mediating the relationship between perceived stress and anhedonia as assessed by the GAME (H5 – 7) and by the TEPS ANT (H10). Finally, we hoped to provide further validation of the newly developed GAME self-report measure of anhedonia by examining its relationship to a commonly used measure of depression: The Beck Depression Inventory II (Beck, Steer & Brown, 1996). We expected the BDI-II to correlate with the GAME so that higher levels of depression were associated with greater levels of anhedonia on the IA, NE and Drive subscales of the GAME, but not on the SP subscale (H11 – 14).

Hypotheses 1, 2 and 4 were supported. Specifically, higher scores on the perceived stress scale significantly predicted greater anhedonia on both the interpersonal pleasure and negative emotionality scales, but did not predict anhedonia in the sensory pleasure domain. Notably, of the significant predictions, only the relationship between perceived stress and negative emotionality survived correction for multiple comparisons. In contrast, perceived stress did not predict anhedonia scores on the drive subscale of the GAME. Thus, hypothesis 3 was not supported. None of the mediation hypotheses for the GAME (H5 – H7) were supported, as perceived stress scores did not predict performance on the line bisection task.

H8 and H9 were supported. Higher perceived stress was predictive of lower anticipatory pleasure, but not consummatory pleasure, as measured by the TEPS. The line bisection task was also related to the TEPS ANT, so that more rightward errors on the task (indicative of relative left cerebral asymmetry) were weakly correlated with greater anticipatory pleasure. The relationships between the TEPS ANT and both the line bisection task and the perceived stress scale were weakly supported by the data (as indicated by their Bayes factors), so caution is advised when interpreting these results. Finally, the mediation model, in which the line bisection task was expected to mediate the relationship between perceived stress and anticipatory pleasure (H10), was not supported, as perceived stress scores did not predict performance on the line bisection task.

The final collection of hypotheses aimed to validate the GAME with a commonly used measure of depression – the BDI-II (Beck, Steer & Brown, 1996). H11 and H12 were strongly supported. Higher depression scores were strongly correlated (.678) with higher levels of anhedonia on the Negative Emotionality (NE) subscale of the GAME (H11). A weak correlation (value?) was also observed between high levels of depression and greater levels of anhedonia on the Interpersonal Anhedonia (IA) subscale of the GAME. In contrast, H13 was not supported. Depression scores were unrelated to novelty seeking aspects of anhedonia, as assessed by the Drive subscale of the GAME. Owing to the consummatory nature of items on this subscale, the Sensory Pleasure (SP) subscale of the GAME was not expected to be related to levels of depression (H14). This hypothesis received moderate support, as indicated by the Bayes Factor.

Putative relationships between relative sensitivity to stress and anhedonia in emotional (H2) and interpersonal (H1) domains reflects several common themes from the literature. The negative emotionality subscale of the GAME is dominated by items pertaining to depression and neuroticism (see table 5.1). In keeping with this observation, moderate to strong correlations have been observed between this sub-scale and the big five domain, neuroticism (see study 2, chapter 4) and with depression (assessed by the BDI-II) in the present study (H12). Meanwhile, the interpersonal pleasure scale of the GAME comprises a series of items related to social and interpersonal activities (see table 5.1). Perceived stress has been linked to an array of both depressive symptoms and aspects of social anhedonia in the literature. For example, Pizzagalli et al. (2007) observed that heightened sensitivity to stress was related to higher levels of both anhedonia and depression, as well as reduced reward responsivity. Honing in on social aspects of reward, Horan, Brown and Blanchard (2007) observed greater levels of perceived stress among participants with higher social anhedonia scores on the Chapman scales. Relative to peers low in social anhedonia, this group perceived similar levels of stress as more unpredictable, uncontrollable or otherwise overwhelming. Finally, paradigms using acute social stressors, e.g. social evaluation, have been linked to higher levels of anhedonia, so that anhedonia predicted reductions in behavioural measures of reward responsivity following the experience of an acute stressor (e.g. Bogdan & Pizzagalli, 2006). Work by Pérez-Edgar et al. (2013) has also linked the experience of an acute social stressor to an increase in attention

toward angry (relative to happy) faces, i.e., in responses to social stimuli. Indeed, recent work by Enneking et al. (2018) using a well-powered fMRI paradigm observed a relationship between volumetric differences in structure of the reward system (specifically, reduced gray matter in the bilateral caudate nucleus) and higher social anhedonia (per the Chapman Social anhedonia scale) in a group of patients with MDD. This relationship was not observed in a control group and the relationship was independent of the depression diagnosis or severity, whether participants were medicated and the course of their disorder. This led the authors to posit that social anhedonia may be a promising marker for depression. Taken together, this work strongly implicates a relationship between perceived stress and anhedonic depression, which may be particularly impacted in the social domain.

As recognition of the heterogeneity of depression has increased, a number of studies have attempted to parse or otherwise dissociate sub-types of the disorder (see, e.g. Treadway & Zald, 2011; 2013). While basic and human neuroscience implicates discrete phases of reward processing, e.g. anticipatory versus consummatory, in this process (see, for example, Kumar et al., 2014; 2015), attempts to develop questionnaire measures sensitive to the individual phases of the reward process have largely failed. For example, the Dimensional Anhedonia Rating Scale (DARS; Rizvi, Quilty, Sproule, Cyriac, Bagby & Kennedy, 2015) was developed expressly to tap desire, motivation, effort and consummatory pleasure. Despite this aim, factor analysis of the questionnaire suggests a four-factor structure reflecting domains of hedonic experience within the following domains: food / drink; hobbies; social activities and sensory experience (Rizvi et al., 2015). Similarly, the GAME was developed based on an exploratory factor analysis of existing questionnaire measures of anhedonia (see chapter 4). Rather than representing discrete phases of reward processing, this scale also collapses onto four factors, reflecting different domains of experience, e.g. social, sensory, emotional and novelty seeking (drive). The division of hedonic experience into these different domains does not accurately reflect the brain-behaviour deficits observed in anhedonia, which typically implicate difficulties in discrete aspects of reward processing, e.g. effort expenditure for reward (Treadway Buckholtz, Scwartzman, Lambert & Zald, 2009), or reward responsivity (e.g. Pizzagalli, Jahn & O'Shea, 2005), compared to relatively preserved consummatory aspects of reward (e.g. Sherdell, Waugh & Gotlib, 2012). There is a clear discrepancy then, between the findings from studies of the brain-

behaviour relationships prioritised by initiatives such as the RDoC and traditional self-report questionnaire measures used to assess phenomena such as anhedonia.

This discrepancy may, in part, explain why our mediation hypotheses were not supported in the present study. In partial support of this argument, the analyses of the relationships between perceived stress and performance on the line bisection task yielded different relationships for anticipatory relative to consummatory anhedonia, as measured by the TEPS (H8 – H10). The TEPS (Gard et al., 2006) is a questionnaire measure that attempts to separate anticipatory and consummatory aspects of hedonic tone. In the present study, both perceived stress and performance on the line bisection task predicted anticipatory pleasure, but not consummatory pleasure. Specifically, higher perceived stress was associated with lower levels of anticipatory pleasure, while a rightward bias on the line bisection task (indicative of relatively greater left frontal activation) was associated with greater anticipatory pleasure. These relationships reflect previous research suggesting that stressors have differential impacts on anticipatory versus consummatory phases of reward processing and that these effects are influenced by individual differences in stress sensitivity. In a series of studies, Kumar et al. (2014; 2015) observed dissociable effects of an acute stressor on anticipatory relative to consummatory stages of reward processing. Specifically, negative social evaluation of the participant's performance on a task resulted in increased mesolimbic activation, particularly the right caudate, and the amygdala. In contrast, during the consummatory phase, activity in the striatum (left caudate and putamen) showed reduced activation. As theirs was a very underpowered study, the results reported by Kumar et al. (2014; 2015) should be interpreted with caution, but they tentatively support the relationship observed between the TEPS and the PSS in the present study, i.e. that stressors attenuate anticipatory, but not consummatory phases of reward processing.

These findings are also in keeping with animal studies indicating that acute stressors can influence approach and avoidance behaviours, whereby an acute stressor will temporarily promote approach motivation, but a stressor that becomes chronic will attenuate this motivation, instead leading to the development of withdrawal motivation (e.g. Cabib & Puglisi-Allegra, 1996; Lemos et al., 2012). One potential mechanism of action for the stress-related effects on discrete phases of reward processing, may be due

to stress-related increases in levels of tonic dopamine, which inhibit firing of phasic dopamine, such as that expected to occur in response to reward prediction errors (Cabib & Puglisi-Allegra, 2012; Kumar et al., 2014). Cabib and Puglisi-Allegra (2012) argue that this increase in tonic dopamine is adaptive in the short-term, as it promotes coping mechanisms. However, the experience of chronic stress, which is appraised as inescapable or overwhelming, results in the attenuation of NAcc dopamine. While this hypothesis remains speculative, it is in keeping with observations of an attenuated feedback-related negativity (FRN; an event related potential EEG component, thought to reflect phasic dopamine firing in response to reward prediction errors) amplitude in patients with heightened levels of anhedonia in response to negative versus positive feedback (Liu, Wang, Shang, Shen, Li, Cheung & Chan, 2014). This attenuation of the FRN seems to be specific to anhedonia and is not common across all participants with MDD (see Mueller, Pechtel, Cohen, Douglas & Pizzagalli, 2015). Furthermore, the FRN response seems specifically linked to trait anticipatory pleasure (assessed by the TEPS) and is unrelated to consummatory pleasure (Cooper, Duke, Pickering & Smillie, 2014). This latter observation is echoed in the relationship between TEPS ANT and rightward bias on the line bisection task ($r = .145$), indicative of relative left asymmetry, observed in the present study (H10). However, this effect did not survive a correction for multiple comparisons and in the Bayesian analysis had a Bayes factor of only 1.6 in favour of the alternative hypothesis. Taken together, this work suggests that if anhedonic depression arises due to stress-induced reductions in dopaminergic transmission, the attenuated FRN observed by Liu et al. (2014) is to be expected. Such reductions are likely linked to deficits in trait approach motivation or anticipatory pleasure and thus frontal asymmetry. Further work is needed to test this putative model, whereby high levels of perceived chronic stress predict both heightened tonic dopamine transmission and attenuation of the FRN, specifically for individuals with lower hedonic tone.

Given this putative relationship between tonic dopamine transmission and frontal EEG asymmetries (see section 1.8.2.5), as well as evidence of the differential effects of stress on NAcc dopamine and approach / withdrawal behaviour (see Cabib & Puglisi-Allegra, 2012), it seems reasonable to expect that heightened perception of stress would attenuate left-lateralised cerebral activation (given previously discussed links between frontal left EEG asymmetry and approach motivation; see section 1.7.1). Prior work

considering stress in relation to frontal EEG asymmetries points to a link between relatively greater right (than left) frontal asymmetry and either an increased response to acute stressors, greater experience of chronic stress or increased stress-related risk for the development of psychopathology. Tops et al. (2005) observed a relative increase in right (compared to left) frontal cortical activity following administration of cortisol, a hormone that increases following exposure to uncontrollable stress (e.g. Dickerson & Kemeny, 2004). Similarly, a group of juvenile rhesus monkeys with high levels of cortisol demonstrated attenuated activity in frontal regions, due to a reduction in right frontal gray matter. These moneys also showed heightened responses to stress and a reduced willingness to approach novel stimuli – an anhedonic behaviour - relative to their low cortisol conspecifics (Short et al., 2014).

Beyond experimental work, studies of chronic stressors, particularly the experience of childhood maltreatment, have also observed associations with relatively greater right than left frontal asymmetry. Hostinar et al. (2017) report an association between the experience of childhood maltreatment and greater right (relative to left) frontal EEG asymmetry. These variables interacted to predict higher levels of inflammation so that relative right asymmetry predicted inflammation in participants who had experienced childhood abuse. Similar work by Tang et al. (2018) points to the potential for trait left (relative to right) frontal EEG asymmetry in moderating the relationship between childhood adversity and the subsequent development of psychopathologies, such as PTSD and depression.

In light of this work, the absence of a relationship between stress and performance on the line bisection task – a proxy measure of frontal EEG asymmetry is surprising (see the above tests of all the mediation hypotheses: H5 -7 and H10). As noted in the introduction, we believe that only one prior study has considered the line bisection task as a proxy for frontal EEG asymmetry in relation to stress (Naylor, Byrne & Wallace, 2015). This study invoked acute stress through a combination of social evaluation and performance pressure on participants' engagement in a motor skill task and reported a subsequent change from rightward to leftward bias on the line bisection task (reflecting relatively greater left and right cortical asymmetry, respectively) in response to the stressor. This finding is in line with EEG paradigms administering acute stressors (e.g. Pérez-Edgar et al., 2013; Tops et al., 2005; Tang et al., 2018).

Several possible limitations may explain the absence of an observed relationship between perceived stress and performance on the line bisection task. First, contrary to prior studies administering the line bisection task as a proxy for EEG asymmetry (e.g. Nash, McGregor & Inzlicht, 2010; Naylor, Byrne & Wallace, 2015), we did not use pen and paper measures, but rather administered the task online. Several crucial aspects of this different format may have impacted participant's performance, making this online line bisection task less reliable than traditional pen-and-paper methods. While it was recommended that participants completed the study in a quiet place on a desktop or laptop computer, we had no control over the conditions in which participants completed the task. This might represent a crucial difference between this version of the online task and that carried out by Stavrou, Cooper and Pickering (2018), who had participants complete the online test in a lecture theatre on laptop computers. Beyond this, while we asked participants to indicate the midpoint of each line by clicking once where they thought the midpoint was, there was nothing to stop participants either adjusting the midpoint or sliding the button across the screen to bisect the line (indeed, participants who completed the task on their smartphones may have had no option but to complete the task in this manner).

Second, it should be noted that the line bisection task is not a particularly well validated index of EEG cortical asymmetry. While the study by Nash, McGregor and Inzlicht (2010) is not the only work that has sought to validate the paradigm with actual EEG resting state data, correlations between the two measures tend to be weak. For example, in the study by Nash, McGregor and Inzlicht (2010), the correlation between the two measures is surprisingly low (0.38), and does not survive correction for multiple comparisons, thus undermining the authors claim that the line bisection task is a valid proxy measure for EEG asymmetry. Similarly, Çiçek, Nalçaci and Kalaycioglu (2003) report small to moderate correlations between performance on the line bisection task and resting state EEG, which were observed for both frontal and posterior regions. Thus, further validation of the relationship between EEG cortical asymmetry and bias on the line bisection task is required before this task can be reliably used as a proxy index.

Third, most of the studies discussed in this chapter have utilised some form of change score in relation to hemisphericity. For example, Naylor, Byrne and Wallace (2015) report the change in leftward to rightward bias on the line bisection task in relation to an acute stressor. Similarly, study 2 by Nash, McGregor and Inzlicht (2010) examines the change in line bisection bias in response to an emotional challenge. The present study opted to use a single index (rather than a difference score) due to the interest in chronic or perceived stress. Thus, in line with prior work considering chronic stress (e.g. Hostinar et al., 2017; Tang et al., 2018), we expected that a single index of trait hemisphericity would related to greater levels of perceived stress.

Several explanations may account for why no such relationship was observed (beyond the aforementioned limitations of the line bisection task). First, with the exception of Kumar et al. (2015), most of the work reporting a relationship between chronic stress and abnormalities in neural indices of reward processing have focused on childhood maltreatment. Childhood maltreatment may be a unique form of chronic stressor and thus may show unique patterns of neural alterations relative to other forms of stressors, particularly linked to the left hemisphere (see Teicher, Andersen, Polcari, Anderson, Navalta & Kim, 2003 for a review). Indeed, in a large sample of 401 active combatants, Moran et al. (2017) observed differential relationships between frontal EEG asymmetry and traumatic life events experienced in adulthood versus childhood adversity. Specifically, childhood maltreatment was linked to relatively greater left alpha power (i.e. increased right cortical activity), whereas adult-experienced trauma was linked to higher right alpha power (i.e. increased left cortical activity). This discrepant association between different stressors and hemisphericity may help to explain heterogeneity in the relationship between post-traumatic stress (PTSD) and EEG asymmetry (see Meyer et al., 2015 for a review). Thus, the focus on perceived stress (rather than the experience of early life stress or, more specifically, childhood maltreatment) in the present study may also explain the absence of an association between stress and performance on the line bisection task.

The PSS scores in the present study were also quite low, suggesting that the sample, as a whole, was characterised by relatively low perceived stress. The mean PSS score for the present sample was 17, which is 5 points lower than that reported by Pizzagalli et al. (2007), although it is in line with normative data on the PSS reported by Cohen and

Janicki-Deverts (2012). In their sample, Pizzagalli et al. (2007) report group differences between individuals high and low in perceived stress in relation to their performance on a preferentially rewarded reward bias task. Participants with higher levels of perceived stress were less likely to develop a bias for the disproportionately rewarded stimulus. Thus, it is possible that reward-related impairments are only evident in participants with relatively high levels of stress and the future work should employ a between-groups design to better capitalise on relationships between high levels of perceived stress and approach related deficits, e.g. greater right relative to left cortical activation.

A final aim of the present study was to offer additional validation for the GAME by using a common self-report measure of depression, the BDI-II, in a new sample of participants (H11-14). Only the IA and NE subscales of the GAME correlated with scores on the BDI-II. The correlation between the interpersonal anhedonia subscale and the BDI-II was weak (.207), undermining claims that social anhedonia can be viewed as a marker for depression (e.g. Enneking et al., 2018). In contrast, the negative emotionality subscale yielded a strong correlation with the BDI-II (.678), most likely reflecting the previously observed overlap between the GAME NE and neuroticism (.737; see study 2, chapter 4) and the well-established links between neuroticism and depression (e.g. Mulder, 2002; Enns & Cox, 1997). Similarly, a moderate-to-strong relationship was observed between GAME NE and scores on the PSS (.630). Again, this is most likely due to the relationship between perceived stress and neuroticism (e.g. Kilby, Sherman & Wuthrich, 2018). Correlational relationships between the GAME subscales and other measures (see table 5.2) suggest weak to moderate correlations with the TEPS anticipatory and consummatory subscales, whereby the GAME Drive and TEPS ANT are moderately negatively correlated (-.48) and the GAME SP yields a moderate negative correlation with the TEPS CON (-.49). These correlations are insufficiently strong to claim that these subscales are measuring identical constructs, but provide some evidence of temporal distinction between the Drive and SP subscales of the GAME. Thus, as both correlations are similar in size, but opposite in valence, it could be that GAME Drive is assessing an anhedonic response analogous to anticipatory pleasure, while GAME SP is likely tapping a similar construct to consummatory pleasure. In contrast, the Interpersonal Anhedonia and Negative Emotionality subscales of the GAME reveal weak correlations with both the TEPS

subscales (r=x and y respectively). This is to be expected, given their relative focuses on social and emotional domains of pleasure.

Finally, the present study raises some points about the psychometric properties of the GAME. This study indicates that further refinement of the measure is necessary for a variety of reasons. First, the internal reliability was lacking for two of the four subscales. Specifically, reliability for Drive was weak (α = .59) and was very poor for the Sensory Pleasure subscale (α = .32). While the MacDonald's Omega is approximately similar across all three samples (i.e. studies 1 and 2 from chapter 4 and the present sample), the Cronbach's alpha for the Drive and – particularly for the SP – subscales is considerably decreased in the present sample. Given the more robust properties of omega (compared to alpha), particularly with respect to violations of tau-equivalence (i.e. the assumption of equal item variance) psychometricians have increasingly advocated for adopting omega in lieu of alpha as a measure of reliability in psychological scale development (e.g. Dunn, Baguley & Brunsden, 2014). This is because, in situations where tau-equivalence is violated, alpha tends to underestimate the reliability of the scale, relative to the population (i.e. true) reliability level. Thus, the relatively low alpha observed for the SP and Drive scales may be less a cause for concern, given that omega outperforms alpha in situations of tau-equivalence violation (Dunn, Baguley & Brunsden, 2014). In accounting for the relatively large decrease in Cronbach's alpha for the SP scale from studies 1 and 2 to the present study, we must bear in mind that the majority of the items that were dropped (based on the modification indices from the CFA: chapter 4, study 2) were from the SP subscale (5 items were dropped from this scale). These items appeared to correlate more strongly with one another than did the remaining items on the revised SP subscale of the 40-item GAME. Furthermore, based on the mean scores per item, questions pertaining to this subscale appeared to have a much lower endorsement relative to the other subscales (see Table 5.3). Based on these psychometric properties, and in consideration of the broadly similar fit indices in the 50- and 40- item GAME, future work using this measure should revert to the full 14-item SP subscale.

As the GAME was developed using existent measures of anhedonia and reward responsivity (see chapter 4), the difficulty in establishing clearer validity for this

questionnaire is troubling and questions the validity of current self-report measures of anhedonia more generally. As noted above, previous attempts to establish a robust questionnaire measure that dissociates different domains of the reward cycle and demonstrates convincing reliability and validity have encountered difficulty, e.g. the DARS (Rizvi et al., 2015; see also chapter 4 for a discussion). The TEPS (Gard et al., 2006) is arguably the most suitable of the currently available measures to adopt in paradigms attempting to substantiate brain-behaviour relationships in anhedonia, as it attempts to parse anticipatory and consummatory aspects of pleasure, however, the factor structure of the TEPS remains under question (see Ho, Cooper, Hall & Smillie, 2015) and the measure needs to be implemented more widely in the literature on depression, which remains largely reliant on outdated consummatory measures such as the SHAPS (see Rizvi, Pizzagalli, Sproule & Kennedy, 2015 for a commentary). The construction and validation of an appropriate measure of anhedonia is crucial as it seems likely that existent measures are insufficiently nuanced to pick up on the brain-behaviour relationships integral to initiatives such as the RDoC (McCabe, 2018).

5.5 Conclusion

This study sought to establish a mediation model of the stress-anhedonia diathesis proposed by Pizzagalli (2014). Specifically, perceived stress was expected to predict anhedonia in social, emotional and novelty seeking domains. It was expected that this relationship would be mediated by relative right cerebral asymmetry (indicated by performance on a line bisection task). Individual differences in perceived stress did predict anhedonia in social and emotional domains, as well as lower anticipatory pleasure. In contrast, no relationship was observed between perceived stress and sensory pleasure, novelty seeking (drive) or consummatory pleasure. The relationship between perceived stress and anhedonia was not mediated by performance on the line bisection task, as this was not predicted by perceived stress scores. Taken together, this work provides tentative support for the relationship between perceived stress and anticipatory deficits in reward processing. It also underscores the need to validate the line bisection task as a measure of cerebral EEG asymmetry and to further develop our understanding of the factor structure of anhedonia.

Chapter 6

Discussion

Overview

This chapter seeks to synthesise the findings presented in the preceding empirical chapters of this thesis. These findings will be linked to the broad aims of the thesis (outlined in chapter 1) and will be contextualised in relation to the wider literature on anhedonia and motivation. Broad limitations of this doctoral programme of research will be discussed. Finally, implications of this work for future research will be outlined.

6.1 Aims of the thesis

The overall goal of this thesis was to consider the measurement of trait-like aspects of approach and withdrawal motivation for reward using a combination of neural, behavioural and psychometric measures. Individual differences in approach and withdrawal motivation have significant implications for a range of psychopathologies, particularly depression. However, most research takes for granted that measures evolving from different theoretical perspectives and assessing discrete aspects of reward processing are broadly tapping similar constructs. In line with recommendations by Reznik & Allen (2018), this thesis advances the literature on anhedonia and frontal alpha asymmetry by examining the evidence for convergent validity between neural, behavioural and psychometric measures of motivated behaviour and anhedonia. Beyond this, the thesis sought to explicitly link approach and withdrawal motivated *behaviours* to putative neural systems hypothesised to underlie motivation via frontal EEG asymmetries (e.g. Davidson, 1992). Finally, this thesis attempted to develop and validate a new psychometric measure of anhedonia. In doing so, the utility of extant psychometric measures of anhedonia has been critically considered.

This thesis sought to examine current assumptions underlying the measurement of approach and withdrawal motivation by pursuing four broad aims, as outlined in the introductory chapter. The thesis attempted to:

1. Integrate behavioural, neural and psychometric measures of approach / withdrawal motivation in the same study to assess the convergent validity of these measures.
2. Examine whether EEG alpha asymmetry can be used as a measure of trait approach and withdrawal motivation.
3. Compare the utility of discrete self-report measures of anhedonia and approach motivation to develop and validate a new self-report measure of anhedonia, which is sensitive to the multifaceted nature of this construct.
4. Consider whether the relationship between discrete components of anhedonia and stress is mediated by a proxy measure of frontal asymmetry.

6.2 Key findings

This section seeks to integrate the key findings from each chapter with the overall aims of the thesis. Each aim will be briefly outlined and the relevant findings from each chapter will be detailed. Following this, the findings will be integrated and briefly discussed in the context of the broader literature on anhedonia and motivation.

6.2.1 Work addressing aim 1

Aim 1: To examine the convergent validity of behavioural, neural and psychometric measures of approach and withdrawal motivation

Chapter 2 sought to address this aim by considering the convergent validity of three putative measures of approach motivation: relative left frontal EEG asymmetry (LFA); performance on the Effort Expenditure for Reward Task (EEfRT; Treadway et al., 2009); and several self-report measures of reward processing: the temporal experience of pleasure scales (TEPS; Gard et al., 2006); the Snaith Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995) and the Behavioural Approach System (BAS) subscale of the BIS / BAS Scales (Carver & White, 1994). This study found limited evidence of convergent validity between the neural (LFA), behavioural (EEfRT) and psychometric (the anticipatory subscale of the TEPS (TEPS ANT) and the reward responsiveness

subscale of the BAS (BAS-RR)) measures. Specifically, no main effect of LFA was observed to predict hard task choices on the EEfRT, however, a significant interaction was observed between LFA and probability of reward receipt on the EEfRT, suggesting that LFA significantly predicted likelihood of choosing the hard task when the probability of reward receipt was low (12%) relative to high (88%).In this respect we broadly replicated prior work by Hughes et al. (2015), who also reported an interaction between LFA and the probability of choosing the hard task on the EEfRT in the 12% (relative to 88%) condition. In contrast, the absence of a main effect of LFA in predicting hard task choices on the EEfRT in the present study is at odds with findings by Hughes et al. (2015). Taken together, the observed interaction is broadly in line with literature implicating the left-lateralisation of dopaminergic process in frontal areas in response to approach motivation and effort expenditure for reward (e.g. Treadway et al., 2012b; Wacker et al., 2013), and with animal work, which suggests that the greatest level of dopaminergic function is observed when reward receipt is most uncertain or unlikely (e.g. Fiorillo Tobler & Schultz, 2003, 2005; Niv, Duff & Dayan, 2005). Beyond this, neither the psychometric measures of consummatory reward - the consummatory subscale of the Temporal experience of pleasure scale (TEPS CON) and SHAPS – nor those addressing anticipatory pleasure – the anticipatory subscale of the TEPS (TEPS ANT) and the reward responsivity subscale of the BIS / BAS scales (BAS-RR) – predicted willingness to expend effort for reward. While this was expected for consummatory measures, anticipatory measures of reward processing were expected to predict EEfRT performance, in line with previously reported findings from Hughes et al. (2015). Taken together, this work queries both the homogeneity of the "anticipatory" or "wanting" phase of the reward cycle, as well as highlighting the lack of convergent validity between diverse measures, putatively assessing approach motivation for reward. Thus, rather than assuming reward "wanting" is one homogenous construct, as the literature commonly suggests (and as is implied by the work of Hughes et al., 2015), the findings from chapter 2 point to a multifaceted anticipatory stage, in which different aspects of the traditional reward "wanting" stage are measured by LFA, EEfRT and the various psychometric measures.

Chapter 3 also sought to address this aim. In contrast to chapter 2, this chapter sought to examine the convergent validity of putative withdrawal motivation. Specifically, the degree to which greater right (relative to left) frontal asymmetry (RFA), a behavioural

measure of loss aversion (see Tom et al., 2007), and the BIS subscale of Carver and White's (1994) BIS / BAS scales, converge in their measurement of withdrawal motivation. Contrary to expectations, no relationship was observed between performance on the behavioural loss aversion task and relatively greater right frontal cortical activation. Instead, a significant relationship was observed between greater loss aversion and right cortical asymmetry at posterior regions. No relationship was observed between the BIS subscale of the BIS / BAS scales and behavioural loss aversion. These findings underscore the need to better characterise withdrawal motivation and its putative links to neural asymmetries. This chapter also highlights the need to move past original conceptualisations of the reinforcement sensitivity theory (oRST; Gray, 1972) and integrate questionnaire measures sensitive to the revised RST (rRST; Gray & McNaughton, 2000) with the EEG asymmetry literature.

Four core implications arise from the work addressing this aim. First, the absence of convergent validity for neural (LFA), behavioural (EEfRT) and self-report (TEPS, BAS) measures of approach motivation is interesting, given the tendency to view these measures as different approaches to the same construct: approach motivation. Building on this observation, a second implication queries whether anticipatory pleasure or the "wanting" stage of the reward cycle is homogenous. Third, the need to better characterise withdrawal motivation and its relation to EEG asymmetry is highlighted. Finally, the need to incorporate the revised RST (Gray & McNaughton, 2000) into the study of EEG asymmetry and motivation is crucial. Two aspects of the RST are of particular relevance here: the need to move away from traditional conceptualisations of BIS as an avoidance mechanism (rather than a means through which goal conflict may be resolved) and the potentially multifaceted nature of BAS (see Krupic & Corr, 2017).

Parsing discrete components of the "wanting" stage of the reward cycle may account for the absence of convergent validity between the neural, behavioural and psychometric measures of approach motivation reported in chapter 2. Prior work by Hughes et al. (2015) report a significant main effect for LFA in predicting hard task choices on the EEfRT. Specifically, they report that individuals with relatively greater LFA at rest were more willing to choose the hard task on the EEfRT, particularly when the likelihood of reward delivery was low (12%) relative to high (88%). Similarly, Geaney, Treadway and Smillie (2015) observed an association with the anticipatory

subscale of the TEPS and willingness to choose the hard task on the EEfRT when the likelihood of reward receipt was 12% (relative to 88%). Based on these observations, we expected to find that both relatively greater LFA and higher scores on the TEPS ANT would predict willingness to expend effort for reward (i.e. choose the hard task) on the EEfRT, especially in the 12% (relative to 88%) probability of reward receipt category.

The absence of a main effect for either LFA or TEPS-ANT in predicting the hard task reflects broader limitations of work adopting the EEfRT. Many studies adopting the EEfRT do not incorporate a self-report measure of anhedonia or reward processing. This is troubling, given discrepancies in the literature linking the EEfRT to other approach-related measures. Inconsistencies in the reward receipt probability bands reported (e.g. 12%, 20%, 50%, 80% or 88%), as well as the self-report measures used and the patterns of relationships between these variables have been fully discussed in chapter 4. Briefly, inconsistent findings have emerged whereby consummatory measures, e.g. the SHAPS, have sometimes been linked to hard task choice on the EEfRT (Yang et al., 2014), but non-significant relationships have also been reported (e.g. Barch et al., 2014; Treadway et al., 2009). Similarly, anticipatory measures, such as the TEPS ANT, have sometimes predicted EEfRT performance (e.g. Geaney, Treadway & Smillie, 2015), but contrary findings have also been reported (e.g. Yang et al., 2014). Finally, contrary to the expected pattern of anticipatory deficits in reward processing, both McCarthy et al. (2016) and Treadway et al. (2012) report an association between greater willingness to expend effort on the EEfRT and more severe symptoms of negative aspects of schizophrenia and depression, respectively.

The absence of convergent validity observed in chapter 2 is understandable in light of such mixed findings. This lack of convergent validity between measures of approach motivation observed in chapter 2 may have many, possibly overlapping, explanations. One putative explanation may be that combining diverse approach-related measures is an inappropriate way to conceptualise reward "wanting". This raises questions about the homogeneity of the "wanting" phase of the reward processing cycle. Clinical diagnoses of anhedonia typically conflate "liking" and "wanting" aspects of reward (e.g. APA, 2013). Such conflation receives little support from the basic science on reward processing (a summary and review is presented by Rømer Thomsen, Whybrow

& Kringelbach, 2015). While much research has stressed this need to parse the anticipatory and consummatory aspects of reward processing (e.g. Gard et al., 2006; Treadway & Zald, 2011), relatively little work has considered sub-domains of anticipatory processes, e.g. effort expenditure for reward, relative to cue evaluation / incentive salience. A relatively novel argument in this area, Zald and Treadway (2017) point to several distinct, but related, phases of reward anticipation, e.g. "wanting" at the subjective level can be conceptualised as urges or cravings, encompassing feelings of both excitement and tension. Behaviourally, in contrast, this stage of the reward cycle manifests in the combined action of perceptual, cognitive, attentional and motor processes to facilitate the achievement of a reward. Typically, anticipatory stages of reward processing are assessed using behavioural strategies that exemplify this reward facilitation, e.g. the EEfRT (Treadway et al., 2009), the Monetary Incentive Delay task (MID; Knutson et al., 2000). Relatively little consideration is given to more nuanced aspects of this process. To this end, Zald and Treadway (2017) point to the utility of behavioural economic concepts, e.g. subjective value, cost and discounting, scaling and reward competition in parsing components of the reward wanting stage. Adopting behavioural measures of these more nuanced aspects of reward processing would help to refine existent self-report and neuroimaging measures, which likely reflect more broad domain-general stages of reward, e.g. consummation, anticipation etc. Similarly, Krupic and Corr (2017) argue for a multifaceted BAS. They identify four sub-components of approach motivation: wanting, incentive motivation, striving and liking and attempt to link these discrete stages to dominant neurotransmitter systems and to broad patterns of personality. These arguments are timely and require further development and empirical tests to establish whether and to what degree anticipatory approach motivation can be conceptualised as a complex multifaceted construct. If approach motivation comprises multiple stages, as these results may indicate, it is increasingly important that we develop new measures – particularly in behavioural and self-report domains – to tap the multifaceted nature of reward "wanting".

The third implication arising from the work addressing this aim is the need to better characterise the relationship between withdrawal motivation and neural asymmetry. A fourth related implication highlights the need to incorporate the revised reinforcement sensitivity theory (rRST; Gray & McNaughton, 2000) into the EEG asymmetry literature. Davidson's (1992) theory posited that withdrawal motivation was linked to

relatively greater right (than left) frontal asymmetry. Thus, approach and withdrawal motivation were argued to have similar, opposing profiles, linked to mania / depression and anxiety. This view continues to permeate the literature today (see Nusslock & Alloy, 2017). Despite its popularity, however, to view of EEG asymmetry as a straightforward marker of approach / withdrawal motivation is undoubtedly an oversimplification. The relationship between withdrawal motivation and right frontal asymmetry has received less research attention (compared to research linking LFA and approach motivation) and many of the findings in this area report mixed results. Many of the discrepancies in this literature may relate to the reliance on Carver and White's (1994) BIS / BAS scales to assess self-reported withdrawal motivation. The BIS / BAS scales were developed based on the oRST (Gray, 1972). Thus, the BIS scale is argued to reflect withdrawal motivation. Early research in this area, e.g. Sutton and Davidson (1997) report a relationship between relatively greater right frontal asymmetry and higher scores on the BIS. However, many studies have been unable to replicate this relationship (e.g. Amodio, Master, Yee & Taylor, 2008; Berkman, Lieberman & Gable, 2009; De Pascalis, Cozzuto, Caprara & Alessandri, 2013; Wacker et al., 2008).

Gable, Neal and Threadgill (2018) review some of this work and, in a crucial contribution to this literature, point to the continued reference to the oRST (Gray, 1972) in the literature on frontal EEG asymmetry. The core change from o- to r-RST in relation to this body of work is the revision of BIS. In oRST, BIS was conceptualised as pathway to withdrawal motivation. In contrast, the rRST views BIS as a mechanism through which goal conflict (between motivational systems, e.g. BAS versus FFFS; BAS versus BAS; FFFS versus FFFS) is resolved (Gray & McNaughton, 2000). The revised BIS, then, works to regulate effortful control, inhibit behaviour, promote self-control and facilitate error detection (Gable, Neal & Threadgill, 2018). Thus, it is necessary to better characterise whether frontal cerebral asymmetry indexes withdrawal motivation or if it is better considered as an indicator of cognitive control. Similarly, the relationship between posterior asymmetry and withdrawal behaviour should be developed further, using modern psychometric measures, sensitive to the rRST, e.g. the reinforcement sensitivity theory personality questionnaire (RST-PQ; Corr & Cooper, 2016).

6.2.2 Work addressing aim 2

Aim 2: To examine whether EEG alpha asymmetry can be used as a measure of trait approach and withdrawal motivation

Aim 2 is closely linked to Aim 1 and reflects Davidson's (1992) theory of motivational direction. According to this theory, anterior cerebral asymmetry is indicative of a propensity to behave in a more approach- or withdrawal-oriented manner, whereby relatively greater left (than right) cortical asymmetry is indicative of heightened approach-related motivation, whereas increased right (relative to left) cortical asymmetry reflects greater withdrawal motivation and avoidance behaviour. This theory has firmly taken hold in the imagination of individual differences researchers, however, evidence to support the theory has been mixed (see, e.g. Wacker, Chavanon & Stemmler, 2010). The majority of studies seeking to characterise the relationship between frontal EEG asymmetry and motivation have relied on Carvery and White's (1994) BIS / BAS scales. In contrast, this thesis sought to link cerebral asymmetry directly to behavioural tasks ostensibly assessing facets of approach and withdrawal behaviour.

Thus, chapters 2 and 3 provide the main tests of this aim. As noted previously, chapter 2 tested whether LFA would predict willingness to expend effort for reward. Effort expenditure for reward is typically considered a core facet of the approach or "wanting" phase of reward processing (see Rømer Thomsen, Whybrow & Kringelbach, 2015). Thus, it was expected that individual differences in LFA would predict willingness to expend greater effort for reward on the EEfRT (Treadway et al., 2009). Contrary to expectations, this relationship was significant only when the likelihood of reward receipt was low (12%) relative to high (88%). The absence of a main effect of LFA may be because all participants were eager to choose the hard task when the probability of reward receipt was relatively high (i.e. 50- or 88 per cent), in contrast, individual differences in effort expenditure for reward might be visible only when the basic incentive to choose the hard task is relatively low (i.e. 12%). As noted in the previous section (6.2.2), these findings question whether approach motivation is a homogeneous construct and, if not, whether frontal EEG asymmetry is an indicator of approach

motivation more broadly (as is popularly thought) or if it reflects a sub-component of this process, e.g. incentive salience or anticipation of an action facilitation response. These findings may suggest that LFA is a neural index of willingness to expend effort for reward, but, reflecting animal work (e.g. Fiorillo Tobler & Schultz, 2003, 2005; Niv, Duff & Dayan, 2005), it may only be apparent under conditions in which willingness to expend effort is not the norm, i.e. when likelihood of reward receipt is low.

Chapter 3, in contrast, sought to test whether relatively greater right (than left) cerebral asymmetry (RFA) would be related to heightened loss aversion on a behavioural gambling task. Loss aversion is a putative avoidance behaviour, characterised by the participant being unwilling to accept a 50 / 50 financial gamble (i.e., a 50% chance of gaining or losing money) unless the amount they stand to gain is larger than that which they stand to lose (Kahneman, 2003). On average, people tend to be loss averse and prior work indicates that most people will only be willing to risk a loss if they stand to gain, on average, twice the amount of the loss (e.g. Haigh & List, 2005; Heeren, Markett, Montag, Gibbons & Reuter, 2016; Johnson & Goldstein, 2003; Post, Van der Assem, Baltussen & Thaler, 2008; Tovar, 2009). Thus, we expected that, in line with Davidson's (1992) theory of motivational direction, RFA would be associated with greater loss aversion on the gambling task. Contrary to expectations, this relationship did not emerge. While greater loss aversion was linked to the right hemisphere, this relationship was characterised by EEG asymmetry at posterior, rather than frontal, sites. This finding is in line with a body of literature which links anxious avoidance to right posterior sites (e.g. Bruder et al., 1997; Heller & Nitschke, 1998; Kentgen et al., 2000).

The findings from these chapters suggest a more nuanced interpretation of the relationship between cerebral asymmetries and approach and withdrawal motivation. Much of the previous research on frontal EEG asymmetries and approach / withdrawal motivation has relied on self-report measures, e.g. the BIS / BAS scales, to assess trait motivation. As noted in chapter 4, the psychometric properties of this questionnaire are questionable, due to its reliance on the out-dated oRST and use of a homogenous BAS (for discussions, see Gable, Neal & Threadgill, 2018; Heym, Lawrence & Ferguson, 1998; Krupic & Corr, 2017). In addition, questionnaires are relatively subjective and ambiguous means of assessing individual differences and may be insufficiently

nuanced to pick up on brain-behaviour relationships, such as those prioritised by the RDoC (see McCabe, 2018 for a brief discussion). In light of the findings from chapters 2 and 3, it is crucial that we refine our measurement of approach and withdrawal motivation to better characterise the nature of EEG asymmetries. This requires the incorporation of a range of behavioural measures of reward processing constructs into paradigms utilising EEG cerebral asymmetry, as well as the incorporation and refinement of psychometric measures sensitive to the rRST. In doing so, we may be able to account for mixed findings in this literature (see Wacker, Chavanon & Stemmler, 2010). Finally, the relationship between right asymmetry and withdrawal motivation has received much less investigation than has LFA and approach motivation. The majority of research seeking to characterise relative right frontal asymmetry and its relationship to withdrawal motivation has studied children (for a review see (Gander & Buchheim, 2015), has reported mixed findings (see e.g. Gable, Neal, & Threadgill, 2018) or has focused on EEG bands other than alpha (e.g. Studer, Pedroni & Rieskamp, 2013). Beyond these complications, differences have emerged in terms of the location of the electrodes linked to putative withdrawal motivation, specifically whether these are posterior or anterior (e.g. Bruder et al., 1997; Heller & Nitschke, 1998; Kentgen et al., 2000), raising the question of whether relative right anterior asymmetry may be better conceptualised as a mechanism for inhibitory control (e.g. Gable, Neal & Threadgill, 2018).

The role of withdrawal motivation in anhedonia is typically underemphasised in the literature. Given the potential importance of chronic mild stress (CMS) models and the acquisition of hopelessness in the development of anhedonic depression (see chapter 5, also Pizzagalli, 2014), greater focus needs to be given to withdrawal motivation in depression. Basic neuroscience research highlights how a depressive phenotype characterised by despair, learned helplessness and a failure to cope can arise in rodents as a result of exposure to CMS (e.g. Cabib & Puglisi-Allegra, 2012). This, in turn, triggers a switch from heightened approach motivation (in response to acute, escapable stress) to increased withdrawal motivation (in response to inescapable, chronic stress) (Lemos et al., 2012). Chapter 5 provides a more in-depth discussion of this mechanism of action, but briefly, chronic inescapable stress inhibits dopaminergic action in the NAcc, and, in turn, promotes dopaminergic activity in the medial PFC (mPFC), relative to an escapable stressor of similar intensity and duration (Cuadra, Zurita, Lacerra, &

Molina, 1999). Dopamine inhibits activity in the mPFC, thus, increased dopaminergic function in this region may reduce mPFC-mediated behaviour, such as the activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis (Maier, Amat, Baratta, Paul, & Watkins, 2006), which plays a key role in mediating an organism's response to stress, particularly the fight or flight response. Previous experience of chronic stress leads to an increase in the response of the mesocortical dopaminergic pathways to an acute stressor, which may reflect the kindling sensitization hypothesis proposed by Post (1992). Owing to regulatory connections between the PFC and NAcc (Del Arco & Mora, 2008), it may be that stress-induced alterations in the mesocortical dopaminergic system, in turn, blunt the release of dopamine in the mesolimbic pathway, thus maintaining reward processing alterations, leading to an anhedonic phenotype.

Recent research emerging from the McCabe lab underscores the relevance of withdrawal motivation in anhedonia. Rzepa, Fisk and McCabe (2017) report attenuated neural responses to aversive stimuli (images of a mouldy drink) at anticipatory, effort and consummatory stages, which parallels deficits in the neural response to reward (images of a tasty chocolate drink) among participants at high- but not low- risk of depression. Similarly, Rzepa and McCabe (2018) highlight a relationship between effort expenditure to avoid aversive stimuli (quantified by a series of rapid button presses – under 6 seconds – to move an on-screen bar away from an image of a mouldy drink) and blunted fMRI neural responses in the precuneus, insula, PFC and putamen in a large sample (N = 84) of adolescents and young adults. This work highlights the relevance of withdrawal motivation in anhedonia, suggesting that the neural bases of anhedonia are not confined to deficits in approach motivation, but that impairments in the avoidance of aversive situations also needs to be considered.

In light of arguments by Zald and Treadway (2017) about the putative utility of behavioural economic constructs in investigating the spectrum of reward processing, loss aversion may be a particularly useful concept to apply to the fuller articulation of withdrawal motivation in anhedonia. Building on the work outlined in chapter 3, effort expenditure paradigms and self-report measures of anhedonia should be built in to loss aversion studies to better characterise withdrawal motivation.

6.2.3 Work addressing aim 3

Aim 3: To compare the utility of discrete self-report measures of anhedonia and approach motivation with the aim of developing and validating a new measure of anhedonia

Findings from chapters 2 and 3 suggested little convergent validity for self-report measures of anhedonia and approach / avoidance motivation when compared with behavioural and neural measures sensitive to these constructs. The weak relationships identified between these measures may underlie conflicting evidence in the literature (e.g. such as those reported by (Wacker, Chavanon, & Stemmler, 2010). Thus, chapter 4 sought to develop a new self-report measure of anhedonia and chapters 4 and 5 attempted to validate this measure.

Despite recent re-conceptualizations of anhedonia as reflective of deficits in primarily anticipatory aspects of reward processing (e.g. Gard et al., 2006; Rømer Thomsen, Whybrow & Kringlebach, 2015; Treadway & Zald, 2011), most self-report measures of the construct focus on consummatory aspects of reward. A host of second generation measures of anhedonia have been developed as an attempt to redress this imbalance. These measures typically attempt either to parse aspects of anhedonia, e.g. the TEPS (Gard et al., 2006) or to provide greater nuance for a specific symptom, e.g. the anticipatory and consummatory interpersonal pleasure scale (ACIPS; (Gooding & Pflum, 2014)). Both these approaches are limited and, based on the work reviewed in chapter 2, insufficiently nuanced to elucidate brain-behaviour relationships in motivation.

Taking existent questionnaire measures of anhedonia and reward processing as a starting point, a list of unique items tapping different elements of reward processing was derived with which to carry out an exploratory factor analysis (EFA) of anhedonia (study 1; chapter 4). The EFA revealed a four-factor structure. A priori expectations were that this factor analysis would converge on domain-specific aspects of reward processing, e.g. social reward, physical reward, food and drink, sex etc. Such an outcome would reflect other attempts at creating a psychometric measure sensitive to the multifaceted nature of anhedonia: The Dimensional Anhedonia Rating Scale

(DARS; Rizvi et al., 2015). Contrary to expectations, the four factors of the GAME instead seemed to reflect a combination of domains of reward experience (the interpersonal anhedonia and sensory pleasure subscales), emotional aspects, most likely linked to low mood aspects of depression (the negative emotionality subscale) and an ambiguous fourth subscale, which we tentatively named drive and which may reflect aspects of novelty-seeking.

Building on the EFA, study 2 of chapter 4 sought to confirm the factor structure of the GAME and to validate this measure using other self-report questionnaires assessing anhedonia and personality. A confirmatory factor analysis (CFA) was run to substantiate the four-factor structure suggested by the EFA. This structure was supported by the CFA. Beyond the CFA, correlational relationships between the GAME and other measures of anhedonia (the TEPS and the SHAPS), a measure of behavioural approach (the BAS subscale of the BIS / BAS scales) and a measure of the big five model of personality (the Big Five Inventory 2; Soto & John, 2017) were examined to provide validation for the GAME. These relationships yielded weak support for an association between any of the GAME subscales and the SHAPS, which was expected, given the latter's emphasis on consummatory pleasure. Moderate correlations were observed between the TEPS CON and the sensory pleasure subscale of the GAME (GAME-SP), likely reflecting the large number of items sensitive to physical or sensory pleasure in the TEPS CON. Similarly, a moderate correlation emerged between the TEPS ANT and the interpersonal anhedonia subscale (GAME IA).

Finally, chapter 5 sought to provide further validity for the GAME by considering its relationship to measures of depression, stress and a proxy measure of cerebral EEG asymmetry, the line bisection task. The results of this study provided limited support for the GAME. While some support for the interpersonal and emotional subscales emerged, due to their strong (NE: r = .68) to moderate (IA: r = .21) significant correlations with a measure of depression (i.e. the Beck Depression Inventory II (BDI-II)), the novelty seeking (Drive: r = 0.07, non-significant) and sensory pleasure (SP: r = .07, non-significant) subscales were not at all related to scores on the BDI-II. In contrast, no relationships were observed between any of the anhedonia measures and

the line bisection task, a behavioural proxy for frontal EEG asymmetry (all *r*s < 0.05, non-significant).

Taken together, these findings raise some interesting implications about self-reported measurement of anhedonia. First, the factor structure of the GAME should be discussed. Theoretically, two discrete factor structures would be logical alternatives for a questionnaire measure of anhedonia. This measure could be expected to reflect either discrete stages of the reward processing cycle, e.g. anticipatory pleasure, consummatory pleasure etc., similar to the TEPS (Gard et al., 2006), or to reflect domains of hedonic experience, e.g. social, sensory etc., similar to the DARS (Rizvi et al., 2015). In contrast, the GAME points to a hybrid structure, which encompasses domains of hedonic experience, i.e. sensory pleasure and interpersonal anhedonia, as well as a somewhat anticipatory subscale, which seems to address novelty seeking (Drive) and, finally, an emotional subscale, which is not reflected in extant measures of anhedonia, but is represented by questionnaires assessing a related syndrome – apathy (Ang et al, 2017).

As a technique, the results of a factor analysis depend very much on the initial ingredients put into the analysis (see Tabachnick & Fidell, 2001 for a brief discussion); i.e. to a great extent, what you get out of the analysis reflects what you have put in. While the factor analyses conducted in the current programme of research were planned a priori, they are still a product of the questionnaire measures used in the original analysis. Several researchers argue that, in order to provide a more representative picture of a construct, factor analysis should not rely only on self-report data, but should also encompass data from life information (e.g. ecological momentary assessment) and objective task data (see Pervin, Cervone, & John, 2008; Trninic, Jelaska & Stalec, 2013). Given the exclusive focus on self-report data in the present study, the factor structure of the GAME should be considered in light of the constructs emphasised in the literature on anhedonia. Thus, the dominance of the Interpersonal Anhedonia factor likely reflects the relative prevalence of social anhedonia in the literature. The Chapman scales (Chapman, Chapman & Raulin, 1976) contain a social anhedonia scale, and several of the second-generation self-report measures of anhedonia either present a nuanced picture of social anhedonia (i.e. the Anticipatory and Consummatory Interpersonal Pleasure Scale – ACIPS; Gooding & Pflum, 2014) or reduce onto a

predominantly social factor (i.e. the Specific Loss of Interest and Pleasure Scale – SLIPS; Winer, Veilleux & Ginger, 2014). Similarly, the original, first-generation anhedonia questionnaires are dominated by consummatory items, thus, the Sensory Pleasure subscale of the GAME – comprising mostly sensation-based consummatory items – likely reflects the high volume of measures sensitive to this construct, despite its relative lack of importance to the current understanding of anhedonia (see Treadway & Zald, 2011).

Interestingly, the Negative Emotionality and Drive subscales of the GAME do not have clear parallels in the extant psychometric literature on anhedonia. It is possible that the Negative Emotionality subscale taps a related construct to anhedonia: low mood. Low mood and anhedonia are the two cardinal symptoms of depression and one of these two symptoms is required in order to obtain a diagnosis of major depressive disorder (APA, 2013). Given the relative importance of these two constructs, it is arguably important to include a measure of low mood in assessing anhedonia in order to clearly discriminate the relative contribution of the two symptoms to an overall depressive phenotype, e.g. it may be possible to see the unique contribution of anhedonia to an outcome, such as stress, by considering the variance accounted for by the Drive, interpersonal anhedonia and sensory pleasure subscales, with negative emotionality partialled out. In order to substantiate this interpretation, further validation of the GAME is needed; in particular, the negative emotionality scale should be validated with a measure of depression. Care should be taken to test the discriminant validity of these subscales explicitly, e.g. in their ability to predict depression, using the refined version of the GAME in a separate sample.

Finally, the Drive subscale of the GAME appears to assess some form of novelty-seeking. Arguably, this reflects the "interest" aspect of the DSM-5 definition of anhedonia, whereby anhedonia is defined as *"A loss of interest and enjoyment in pleasurable activities"* (APA, 2013, p. 163). Thus, Drive could be considered as an aspect of anticipatory pleasure or the "wanting" stage of the reward cycle. In support of this idea, a moderate correlation (-.48) was observed between the Drive subscale of the GAME (scored to reflect anhedonia) and the anticipatory subscale of the TEPS (scored to reflect anticipatory pleasure) in chapter 5. This relationship is insufficiently strong to warrant the suggestion that the GAME Drive is a pure measure of anticipatory

anhedonia, but could be viewed as support of the role of novelty-seeking as part of a multifaceted "wanting" stage (see Krupic & Corr, 2017).

The GAME represents an advance on existent questionnaire measures of anhedonia due to its ability to parse discrete aspects of reward processing beyond basic elements of physical and consummatory reward (e.g. the Chapman scales) or crude boundaries of anticipation and consummation (e.g. the TEPS). This is important, as, in line with research incentives such as the Research Domain Criteria (RDoc), it is likely that different psychopathologies demonstrate different patterns of association with reward processing deficits and other outcome variables, e.g. stress. Recent work by Ang et al. (2018) highlights the importance of taking a multidimensional approach to reward processing deficits. Apathy is a syndrome essentially synonymous with anhedonia, in that it refers to disordered motivation, characterised by reductions in self-initiated goal-directed behaviour (Marin, 1991). The newly developed Apathy Motivation Index (AMI; Ang et al., 2017) reveals a three-factor structure, which partly overlaps with that of the GAME. The AMI yields Social, Emotional and Behavioural factors; the social factor maps onto the Interpersonal Anhedonia factor of the GAME, while the Emotional factor demonstrates considerable overlap with the GAME Negative Emotionality subscale (see chapter 4 for a more detailed discussion). Using the AMI, Ang et al. (2018) showed that behavioural and social apathy were relatively impaired in participants with Parkinson's Disease (relative to healthy controls), while emotional apathy remained relatively preserved. Such patterns of multidimensional apathy are unlikely to be unique to Parkinson's Disease, but may be differentially affected in other reward processing disorders, including depression. Unique impairments in discrete aspects of reward processing have important implications for treatment (e.g. Akil et al., 2018; Cipriani et al., 2009; Rush et al., 2006) and thus, underscore the importance of developing new measures sensitive to the multifaceted nature of anhedonia.

6.2.4 Work addressing aim 4

Aim 4: To consider whether the relationship between discrete components of anhedonia and perceived stress is mediated by a proxy measure of frontal cerebral asymmetry

Chapter 5 sought to provide a test of the model of stress and anhedonia proposed by Pizzagalli (2014). In this article, Pizzagalli argues that chronic stress, which is perceived to be inescapable, prompts the onset of anhedonia by modulating dopaminergic mechanisms in the Nucleus Accumbens (NAcc). The inhibition of NAcc Dopamine by chronic stress leads to the cessation of approach motivation and increases withdrawal motivation, i.e. avoidance of the stressor (Lemos et al., 2012). While chronic stress inhibits of NAcc dopamine, it promotes the activity of dopamine in the medial prefrontal cortex (mPFC; Cuadra, Zurita, Lacerra, & Molina, 1999). Thus, we sought to examine whether perceived stress, assessed using the perceived stress scale (PSS; Cohen, Kamarck & Mermelstein, 1983) would predict anhedonia. We were particularly interested in whether PSS scores would be specifically related to anticipatory aspects of anhedonia (i.e. the anticipatory subscale of the TEPS), as well as social, emotional and novelty-seeking aspects of anhedonia (i.e. the Interpersonal Anhedonia, Negative Emotionality, and Drive subscales of the GAME). In contrast, we expected that PSS scores would be unrelated to consummatory aspects of anhedonia (i.e. the consummatory subscale of the TEPS and the Sensory Pleasure subscale of the GAME). Beyond this, we expected that relatively greater right cortical activity (indexed by a leftward bias on the line bisection task – a proxy measure of EEG asymmetry) would mediate the relationship between perceived stress and anhedonia. In line with the hypotheses, perceived stress predicted anhedonia in anticipatory, interpersonal and emotional domains, but not in consummatory or sensory pleasure domains. Contrary to expectations, cerebral asymmetry (measured by leftward bias on the line bisection task) did not mediate any of these relationships, as perceived stress did not predict performance on the line bisection task.

The relationship between stress and discrete aspects of anhedonia is interesting in view of the work by Ang et al. (2018) highlighting specific patterns of motivational impairments linked to certain neuropsychiatric disorders. A recent special issue of the journal *Current Opinion in Behavioural Sciences* (Husain & Pryce, 2018) highlights

the centrality of motivational impairments, i.e. anhedonia / apathy, to a range of neurological and psychiatric disorders, e.g. depression, schizophrenia, Alzheimer's disease, frontotemporal dementia, Parkinson's Disease and motor neuron disease. Although disordered motivation is a core feature of these disorders, neuroscientific work increasingly points to different patterns of reward processing dysfunction that characterises motivational deficits in specific disorders. A recent review by Lambert et al. (2018) highlights distinctions in patterns of anhedonia between schizophrenia and depression. Specifically, depression is characterised by impairments in anticipatory pleasure, the development of reward-related associations and the integration of reward-related information based on prior experience. In contrast, patients with schizophrenia demonstrate a disorganisation – rather than an impairment – of reward processing and reward-related cognition. Specifically, patients with schizophrenia tend to expend effort for reward in an inappropriate manner (i.e. not conducive to maximising reward and minimising effort) and tend to focus on irrelevant cues (rather than those that will maximise the likelihood of receiving a reward). Given the distinct profiles of reward processing impairments implicated in these disorders, it is thus possible that similar motivational deficits – broadly termed anhedonia or apathy – may arise via disparate neural and psychopathological mechanisms, e.g. effort expenditure impairments in schizophrenia may be driven by dysfunctional cognitive control, whereas similar deficits in depression might arise from a reduction in responsivity to reward and impairments in reward-related learning (see, e.g. Culbreth, Moran & Barch, 2018). In addition, given the well-established heterogeneity of disorders such as depression and schizophrenia (e.g. Treadway & Zald, 2011), it seems equally likely that distinct profiles of depression (and schizophrenia) may have unique patterns of motivational impairments that can be used as markers for disorder prognosis and treatment (this is similar to the argument put forward by Ang et al., 2018).

If unique patterns of motivational impairments can typify subtypes of depression, it seems likely that they will be linked to the causal mechanisms underlying development of the disorder. The evidence from chapter 5 – that perceived stress is linked to certain aspects of anhedonia – is in line with this hypothesis. Pizzagalli (2014) argues that exposure to chronic inescapable stress is a likely mechanism through which a subtype of depression, characterised by anticipatory deficits in reward processing, may arise. In keeping with this notion, we observed that higher scores on a measure of perceived

stress were related to higher levels of anhedonia in interpersonal, emotional and anticipatory domains, but not in consummatory or sensory pleasure domains. This suggests that individual differences in the perception of the chronicity and inescapability – the essential "stressfulness" – of stressors is related to our capacity to initiate and enjoy pleasurable experiences, particularly in interpersonal domains, and to our emotional wellbeing (assessed by the Negative Emotionality subscale of the GAME). While hypotheses surrounding a putative causal relationship between stress and depression have permeated the scientific literature for decades (e.g. Brown & Harris, 1978), a convincing mechanistic account of how stress might cause depression is lacking. The hypothesis put forward by Pizzagalli (2014) is an important step in explaining this processing, however, this causal pathway from stress to anhedonic depression requires empirical validation.

A related body of work has considered the role of inflammation in the development of depression (e.g. Felger & Treadway, 2017; Raison, Felger & Miller, 2018). Similar to the argument put forward by Pizzagalli (2014), researchers in this area argue that inflammation may prompt changes in dopaminergic corticostriatal reward circuity, which may in turn trigger symptoms of anhedonia and, subsequently, lead to the development of depression (Felger & Treadway, 2017). The mechanistic account through which inflammation may trigger depression shows considerable overlap with that proposed by Pizzagalli (2014) (see chapter 1). Recent research has provided a bridge between these theoretical perspectives by linking higher levels of inflammation (i.e. inflammatory markers called cytokines, such as IL-6) in individuals who have experienced early life adversity, a form of chronic, inescapable stress (e.g. Hostinar et al., 2017; Tang et al., 2018), behavioural deficits in reward processing (e.g. Boyle et al., 2018) and a putative role for right (relative to left) cerebral asymmetry in mediating the response between chronic stress exposure and the development of psychopathology, including depression and PTSD (Hostinar et al., 2017; Tang et al., 2018).

Work in this area is in its infancy, but again underscores the need for measures of anhedonia that are sensitive to the multifaceted nature of reward processing. This putative stress / inflammation pathway to depression is likely to affect only a subgroup of individuals exposed to chronic stress and / or inflammation. Supporting this argument, following the experimental administration of the inflammatory marker, INF-

α, increases in depressive symptoms were only observed in 30-50% of patients, undermining the ability of inflammation to account for the development of all depressive episodes (Raison, Capuron & Miller, 2006). Thus, it seems likely that inflammation and stress induce a subtype of depression, which may be better characterised by a specific symptom phenotype, e.g. anhedonia (Raison & Miller, 2011). In order to fully test this hypothesis, additional work needs to parse discrete reward processing impairments arising as a result of heighted inflammation and chronic stress and associate such impairments with specific psychopathologies, e.g. depression, schizophrenia or PTSD.

6.3 Limitations of the work presented in this thesis

A number of limitations should be acknowledged with respect to the work in this thesis. Two core limitations will be outlined with respect to: power and sample size and the conceptualisation and measurement of frontal EEG. These limitations will be briefly outlined and discussed in relation to the work presented in this thesis.

6.3.1 Power, sample size and reproducibility

Failure to conduct a systematic a priori power analysis for all studies represents a key limitation of the work in this doctoral programme of research. In lieu of this, estimates of adequate sample size were based on prior studies using the EEfRT (chapter 2), and frontal EEG (chapter 3), as well as broad rules of thumb concerning adequate sampling for factor analysis techniques (chapter 4, studies 1 and 2), as power analyses for structural equation models are not commonly used. In part, this reliance on prior studies to guide judgements about sampling is due to the inherent difficulty of conducting power analyses for EEG studies (chapters 2 and 3). For standard experimental designs, e.g. utilising a between groups ANOVA, freely available software exists to enable the calculation of adequate power, e.g. G*Power (Faul, Erdfelder, Buchner & Lang, 2009). In contrast, for work using neuroimaging paradigms, no such software currently exists. This is problematic, as EEG data are complex and statistical power is inherently more difficult to quantify for EEG studies, e.g. as the amount of noise in the data cannot be predicted a priori, deciding whether to prioritise the number of trials recorded versus

the number of participants in the study. The EEG studies reported in this PhD are by no means unusual for not reporting power analyses. Rather, this is the norm in EEG research. Larson and Carbine (2017) carried out a systematic review of 100 randomly selected EEG and ERP studies, published in six high impact journals that frequently publish EEG work. None of the 100 studies reviewed reported a sample size calculation, nor did they provide sufficient information to enable the calculation of future sample sizes (e.g. based on variance and correlations among repeated measures). The difficult in calculating these indices and the lack of a unified effort to is particularly concerning in light of the recent reproducibility crisis and given reports of the low statistical power, lack of reproducible results and overestimates of effect sizes in neuroscience (Button et al., 2013). Such issues undermine the conclusions of much existent research in neuroscience and psychology and point to a greater need to establish clear guidelines for good practice in EEG research and the promotion of open science and collaborative efforts toward the collection and sharing of data (see Cohen, 2017; Larson, & Moser, 2017; Smith, Reznik, Stewart & Allen, 2017; Wacker, 2017).

6.3.2 Methodological issues in frontal EEG asymmetry

In a similar vein, Smith et al. (2017) point out the high level of diversity in how frontal EEG asymmetry is quantified and analysed. The body of work considering the role of frontal EEG asymmetry in motivation, reward and psychopathology spans approximately 40 years. Throughout this time several methodological concerns have been raised with respect to this literature (see, e.g. Davidson, 1988; (Hagemann, 2004); Allen & Reznik, 2015). These issues are manifold and encompass both sample-specific points, e.g. the sex and handedness of participants, as well as the comorbidity / heterogeneity of psychiatric disorders, and EEG-specific points, e.g. the choice of reference electrode, the subjectivity of data cleaning, the length of the recording and the use of a state manipulation versus trait recording.

Some of these issues can be applied to the EEG studies discussed in chapters 2 and 3 of this thesis. While we deliberately screen participants to exclude any history of psychiatric illness, our samples were heterogeneous in terms of gender (chapter 2: 36 / 52 participants were female; chapter 3: 23 / 40 participants were female). Despite this, gender was not observed to have a moderating effect on the relationship between frontal

asymmetry and loss aversion (chapter 3), though this analysis was under powered and results should be viewed with caution.

Beyond sample characteristics, we attempted to employ best practice in our approach to the EEG recording. We recorded the data using relatively inactive reference sites, i.e. two reference electrodes were placed one on the lobe of each ear (chapter 2) and one was placed on the left mastoid (chapter 3). Artifact rejection and data cleaning in EEG are inherently subjective practices. In an attempt to counter this subjectivity, the EEG power spectra for both studies (chapters 2 and 3) were calculated independently by two researchers and no significant differences were found between the subsequent alpha asymmetries indices calculated for participants. Thus, we can be reasonably confident that idiosyncrasies in the data cleaning have had little influence on the findings reported in these chapters. For the LFA – EEfRT study (chapter 2), we used a standard resting state recording procedure (i.e. 8 minutes of resting state data collection, during which the participants alternated between one minute sitting with their eyes open and one minute sitting with their eyes closed). In contrast, the loss aversion study (chapter 3) used a non-standard recording length. This study attempted to conceptually replicate work reported by Gianotti et al. (2009) and thus participants were asked to alternate between keeping their eyes open for 20 seconds and closed for 40 seconds to keep our procedure as close to Gianotti et al. (2009) as possible. In total, this left us with 160 seconds of resting state data, from which the EEG asymmetry indices were derived. Although this is below the standard recording time in the area (i.e. 8 minutes), previous work (e.g. Hagemann et al., 1998) reports excellent reliability (Cronbach's alpha = 0.80 – 0.90) from 4 minute recordings, suggesting that shorter durations of resting state recordings may be acceptable.

A final consideration here is the use of state manipulations versus trait-like resting state recordings in the calculation for frontal EEG asymmetries. The literature on frontal EEG asymmetries can be divided into those studying "frontal activity", i.e. data recorded while a participant is in a resting state and thought to reflect reasonably stable trait-like attributes, and those examining frontal "activation", i.e. some change in frontal activity due to a task or state manipulation. Debate exists in the literature as to whether EEG asymmetry reflects state-like or trait-like effects and whether putative trait effects are best assessed during the resting state or during a manipulation of some

form (see Harmon-Jones & Gable, 2017 for a recent review). In line with the majority of studies in the area, this thesis examined frontal asymmetry at resting state, as a putative marker of approach (and withdrawal) motivation (see Smith et al., 2017). A limitation of the work presented in this thesis is the failure to include a state manipulation in any of the studies considering putative cerebral asymmetries (i.e. chapters 2, 3 and 5). Situational manipulations, e.g. pictures of motivationally significant stimuli (Harmon-Jones & Gable, 2009), manipulation of positive affect (Harmon-Jones, Harmon-Jones, Fearn, Sigelman & Johnson, 2009) and body posture, i.e. asking participants to learn forward; a posture that arguably embodies approach motivation (Harmon-Jones, Gable & Price, 2011) report reasonably reliable influences on frontal cortical asymmetry. In contrast, a meta-analysis by Wacker, Chavanon and Stemmler (2010) reported that the association between self-reported BAS and frontal left asymmetry is much weaker and less consistent than is typically assumed. Despite this, prior work by Hagemann et al. (2005), assessing resting state stability in healthy participants on three separate occasions, suggest that approximately 60 per cent of the variance of resting state EEG asymmetry is due to stable trait-like effects, whereas the remaining 40 per cent is influenced by sporadic, state-based influences. Thus, while relatively stable trait-like influences may account for most of the variance in frontal EEG asymmetry, future work would do well to clearly contrast how stable trait-like aspects of frontal asymmetry interact with approach and withdrawal motivation, distinct from and under the influence of state-based manipulations.

6.4 Building on the thesis: recommendations for future work

Taken together the results of this programme of research point to a need to better characterise the measurement of anhedonia as a multidimensional construct. It is particularly important to a) parse discrete aspects of the anticipatory or "wanting" stage of reward processing and b) better characterise the nature of withdrawal motivation in anhedonia. Beyond characterising anhedonia, there is a need to establish mechanistic accounts of how anhedonia may arise and the discrete profiles of reward processing impairments that distinguish anhedonic depression, both from other subtypes of depressive disorder, and from neuropsychiatric disorders characterised by impairments in reward processing, e.g. Parkinson's Disease. This section will briefly outline a

starting point from which we can work toward providing a clearer characterisation of anhedonia.

Efforts to advance the literature on anhedonia – and reward processing more generally – are limited in two core ways. First, there is an over-reliance on self-report measures, which are often out-dated (e.g. the BIS / BAS scales; Carver & White, 1994) or overly nuanced (e.g. the Anticipatory and Consummatory Interpersonal Pleasure Scale; ACIPS; (Gooding & Pflum, 2014). Second, insufficient attention has been given to behavioural tasks and how these constructs converge onto psychometric and neural measures ostensibly assessing the same thing. As indicated by the results presented in chapter 2 of this thesis, the assumption that widely used neural, behavioural and psychometric measures will converge may be misguided and potential discrepancies in measurement impede the progress of the field.

Underlying many of these issues is the reliance of the anhedonia literature on basic neuroscience models of reward processing. As recently discussed by Slaney, Hales and Robinson (2018), typically used rodent tasks, e.g. the sweet taste test, the progressive ration task etc., are surprisingly limited in their translational validity. A full discussion of this literature is beyond the scope of this section (for recent reviews see Der-Avakian & Pizzagalli, 2018; Sheggi, De Montis & Gambarana, 2018; and Slaney, Hales & Robinson, 2018), however, some core tasks and their translational validity will be outlined. Many traditional animal models of anhedonia have focused on impaired consummatory reward processing, e.g. the sweet taste test (Willner, Towell, Sampson, Sophokleous & Muscat, 1987). In such paradigms, the animal's relative preference for a weak sucrose (or saccharin) solution over plain water is the variable of interest. Rodents induced into an anhedonic state (e.g. through exposure to chronic mild stress) typically demonstrate an attenuated preference for the sweet taste (compared to plain water), which is unrelated to the relative calorie content of the liquids and does not reflect an overall decrease in the volume of liquid consumed (e.g. Willner, Muscat, & Papp, 1992). In line with this research and with traditional definitions of anhedonia reflecting a loss of pleasure (Ribot, 1896), most first-generation questionnaire measures of anhedonia emphasise changes in consummatory pleasure (e.g. the Fawcett Clark Pleasure Scale; Fawcett, Clark, Scheftner & Gibbons, 1983). This emphasis has since proven misguided. First, not all animal models of depression lead to a lack of preference

for the sweet taste (see Der-Avakian, Barnes, Markou & Pizzagalli, 2016). Second, human analogues of the sweet taste test fail to show decreased liking for sweet water (relative to plain water) in humans with depression or schizophrenia, irrespective of their self-reported levels of anhedonia (Berlin, Givry-Steiner, Lecrubier & Puech, 1998; Dichter et al., 2010).

Beyond consummatory pleasure, animal models of anhedonia have considered impairments in motivational or reward "wanting" processes. Such tasks show slightly better translational validity than consummation-based tasks, but core limitations remain. First, reflecting limitations in consummatory reward processing, human assessment of reward "wanting" is relatively limited and has relied predominantly on self-report questionnaires (e.g. the TEPS; Gard et al., 2006). Similarly, while animal models of reward "wanting" have utilised an array of tasks, e.g. effort expenditure for reward tasks, progressive ratio tasks, and these tasks have been adopted across several labs, human analogues have been slow to develop and are not widely utilised.

Two behavioural tasks, ostensibly assessing reward "wanting", have achieved some translational success. The effort expenditure for reward task (EEfRT; Treadway et al., 2009) has been widely adopted since its inception and has been used in a number of different labs and with an array of populations. The EEfRT parallels basic neuroscience work by Salamone et al. (2007), which is fully outlined in chapters 1 and 2. Briefly, animals are presented with two options: expend a relatively greater amount of physical effort (e.g. by climbing over a barrier) to obtain a more palatable food reward, or expend minimal physical effort to obtain a freely available, but less tasty, food. A substantial body of work demonstrates that both humans and rodents in their healthy state will work harder to obtain relatively greater rewards (e.g. Salamone et al., 2007; Treadway et al., 2009). In contrast, rats with dopamine depletion will show an increased preference for the freely available, less tasty food (see Salamone et al., 2016) and humans who have ingested amphetamine (promoting levels of extracellular dopamine) demonstrate a greater willingness to expend effort to obtain reward, particular under conditions when reward receipt is unlikely (i.e. 12% relative to 88%; Wardle, Treadway, Mayo, Zald & de Wit, 2011). While this task displays relatively good translational validity, it is hampered by the increased response time taken to achieve the high effort reward (e.g., in the EEfRT this results in a 21-second wait to obtain the

"large" reward, relative to a 7-second wait to obtain the "small" reward). Thus, the organism's tolerance for delay discounting may represent a confound to the behavioural outcome.

Earlier work seeking to characterise reward "wanting" utilised progressive ratio (PR) paradigms. Animal versions of these tasks require rodents to perform progressively greater effort (e.g. an increasing number of lever presses) over a series of trials in order to obtain the same level of reward. The variable of interest in this paradigm is the animal's "breaking point", i.e. the point at which the rodent will cease to work for the reward. Mirroring work using effort expenditure paradigms, the PR task demonstrates reasonable translational validity. Both humans and rodents with pharmacologically depleted dopamine demonstrate a lower breaking point on the PR task (i.e. decreased motivation or reward "wanting"; Aberman, Ward & Salamone, 1998; Barrett et al., 2008; Cawley et al., 2013). Similar to the effort expenditure paradigms, the upper limit of performance on the PR task requires the organism to wait a relatively longer duration to obtain their reward, thus individual differences in the organism's tolerance for delayed reward may interact with their motivation on this task.

Relatively little work has explicitly considered learning across the reward cycle. This is troubling, as advances in human paradigms highlight the need to consider reward-related cognition and affective biases in disordered reward processing (for a discussion see Slaney, Hales & Robinson, 2018). An important exception to this trend is the probabilistic reward learning task (PRLT, e.g. Der-Avakian, D'Souza, Pizzagalli & Markou, 2013; Pizzagalli, Jahn & O'Shea, 2005), which boasts strong translational validity. In this task, participants (human or rodent) are afforded a choice between two behavioural responses. One response is rewarded 80 per cent of the time (the "rich" response), whereas the other response does not result in a reward 80 per cent of the time (the "lean" response). Conversely, both rich and lean responses result in unpredicted feedback (i.e. no reward or reward, respectively) 20 per cent of the time. Healthy participants learn to develop a response bias for the disproportionately rewarded (target) response. In contrast, human participants with high (relative to low) levels of depression and anhedonia fail to demonstrate a bias for the disproportionately rewarded stimulus (Pizzagalli, Jahn & O'Shea, 2005). Similarly, rodents with pharmacologically attenuated dopamine transmission failed to show a bias for the target stimulus, whereas,

rodents who ingested amphetamine (which enhances the striatal dopaminergic response) demonstrated an increased response bias toward the target stimulus (Der-Avakian et al., 2013).

On the surface, these behavioural tasks appear to assess all stages of the reward cycle, as outlined, e.g. by Rømer Thomsen, Whybrow and Kringlebach (2015). However, this work is undermined by two core limitations. First, little work has sought to directly compare task performance across species (Der-Avakian & Pizzagalli, 2018). This limits the translational validity of all the tasks discussed above, as we cannot confidently claim to be assessing similar outcomes in humans and rodents. Second, and of particular interest in view of the results emerging from this thesis, there is a dearth of work considering how performance on these tasks relate to one another. As we increasingly accept the multifaceted nature of reward processing and the potential for discrete patterns of impairments in reward related behaviours both within and between disorders, it is necessary to develop our understand of how the stages of the reward cycle relate to one another. A patient may report a loss of interest in previously pleasurable activities, but this loss may arise from impairments in one or more of the phases of the reward cycle, e.g. inability to initiate goal-motivated behaviour, a deficit in integrating reward-related feedback, or a loss of hedonic response to a reward. Given the relative limitations of self-report and neuroimaging paradigms to parse this information, a comparison of individual differences in performance on array of behavioural tasks, such as those outlined above, suggests a good starting point for the better characterisation of the reward cycle. Building on this foundation of behavioural work, the integration of multi-dimensional self-report measures, such as the GAME, may allow us to utilise psychometric measures in a manner that better reflects the multifaceted nature of anhedonia.

In summary, the implications arising from the work presented in this thesis underscore the multidimensional nature of anhedonia and the need to better characterise discrete phases of the reward processing cycle and how these phases relate to one another and to individual differences in self-reported anhedonia. A key starting point for this work is to return to basic neuroscience models of the stages of reward processing, i.e. anticipatory, effort expenditure and consummatory pleasure. It is important to develop human analogues for the animal models that form the foundation of the work on reward

processing and to examine how performance on these tasks are associated with individual differences in anhedonia in human participants.

6.5 Conclusion

This chapter summarised the main findings from the four experimental chapters of the thesis. In integrating these findings, a core implication emerged: the need to better characterise anhedonia and motivational deficits. Specifically, it seems likely that the current understanding of anhedonia as deficits in reward anticipation or "wanting" is oversimplified. Not only is the anticipatory stage of reward processing likely to be a multifaceted construct, but anhedonia is also likely to involve aberrant withdrawal (as well as approach) motivation. The implications of these findings and the limitations of extant psychometric and neuroimaging measures suggest a need to return to basic neuroscience models of reward processing, including the sweet taste test, effort expenditure and probabilistic reward learning paradigms. Human analogues of these rodent tasks should be developed in line with the guidance specified by Sheggi, De Montis and Gambarana (2018) to ensure maximal translational validity. An examination of individual differences in performance across these tasks is a core direction for future research, as this will help clarify the nature of the reward processing cycle and parse broad domains, such as anticipation, into more nuanced sub-components.

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Appendices

Appendix A: Article based on Chapter 3

Reference: Duke, É., Schnuerch, R., Heeren, G., Reuter, M., Montag, C. & Markett, S. (2018). Cortical alpha asymmetry at central and posterior – but not anterior – sites is associated with individual differences in behavioural loss aversion. *Personality and Individual Differences*, 121, 206 – 212.

Cortical alpha asymmetry at central and posterior – but not anterior - sites is associated with individual differences in behavioural loss aversion

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Abstract

Heightened sensitivity to losses, known as loss aversion, is a putative avoidance behaviour, which commonly influences decision-making, particularly in economic scenarios where participants have a 50/50 chance of winning or losing money. Evidence from neuropsychology, EEG and TMS research suggests individual differences in loss aversion may be explained by neural differences in the lateralisation of the right hemisphere. 40 healthy participants underwent an EEG recording during resting state and subsequently performed a behavioural loss aversion task, in which they had an equal chance of winning or losing money. EEG asymmetry in the alpha band at central and posterior sites was associated with individual differences in behavioural loss aversion. This asymmetry was driven by a combination of increased activation in the right hemisphere and decreased activation in the left hemisphere and the site of this asymmetry differed for females and males. These findings are discussed in relation to behavioural avoidance.

1. Introduction

1.1 Behavioural loss aversion

Human decision making is subject to bias from a range of spurious influences, not least our personality traits and emotional states. Prospect theory (Kahneman & Tversky, 1979) attempts to account for some of these influences and, in turn, individual differences in decision making. A key suggestion of this theory is that individuals are loss averse, that is, we overweight the negative impact of losses in comparison to the positive impact of gains. Research by Kermer et al (2006) indicated that participants overestimated the negative impact of monetary loss on their mood both in the immediate aftermath of the loss and at a later time compared with actual variation in mood following a financial loss. In-keeping with this notion of loss aversion, most people will only accept a 50/50 financial gamble (i.e., a 50% chance of gaining or losing money) if the amount they stand to gain is at least twice as large as that they stand to lose (Kahneman, 2003).

Behavioural loss aversion is traditionally measured using a series of mixed gambles that vary in the magnitude of gains and losses (e.g., Tom et al., 2007). Loss aversion is typically calculated by the mathematical parameter Lambda (λ), using the formula: $\lambda = -\beta_{loss} / \beta_{gain}$. Both β values are obtained from a logistic regression used to predict the decision made, with gain and loss amounts used as predicting variables. Studies of behavioural loss aversion typically report a λ with a mean value of 2, in-keeping with participants' double-weighting of losses compared to gains (Haigh & List, 2005; Heeren, Markett, Montag, Gibbons & Reuter, 2016; Johnson & Goldstein, 2003; Post, Van der Assem, Baltussen & Thaler, 2008; Tovar, 2009). However, slightly lower values have also been observed (e.g., Frydman, Camerer, Bossaerts & Rangel, 2011; Sokol-Hessener et al., 2009), potentially reflecting methodological variations in the choices offered to participants.

1.2 Loss aversion and the right hemisphere

Neuropsychology research supports the involvement of the right hemisphere in risky decision making, suggesting that individual differences in the neural functioning of the right hemisphere may underpin variation in behavioural loss aversion. Patients with acquired injuries to frontal brain areas tend to exhibit a preference for risky decisions with little regard for potential negative consequences, suggesting diminished or absent loss aversion (Rahman, Sahakian, Cardinal, Rogers & Robbins, 2001). This effect is pronounced for lesions to the right hemisphere, particularly in the right ventromedial prefrontal area (Clark, Manes, Antoun, Sahakian & Robbins, 2003; Tranel, Bechara & Denburg, 2002). This involvement receives support from neuroscientific research by Knoch et al (2006a), who found that healthy participants made riskier decisions on a gambling task after the application of transcranial magnetic stimulation (TMS) to disrupt the right dorsolateral prefrontal cortex (PFC). This effect was not observed when TMS was applied to the left dorsolateral PFC.

1.3 EEG alpha asymmetry and reward sensitive behaviour

Researchers have sought to characterise the source of loss aversion by considering how individual differences in neurobiological traits reflecting reward sensitivity can influence decision making. The hemispheric asymmetry of tonic prefrontal activity, assessed using resting-state electroencephalography (EEG), is thought to be a relatively stable index of behavioural approach and avoidance (Davidson, 2004; Harmon-Jones, Gable & Peterson, 2010; Tomarken et al., 1992). Tonic cortical activity is typically quantized by measuring the power of alpha-band (8-13 Hz) oscillations (see, e.g., Davidson, 1992). Alpha-band oscillatory activity reflects cortical hypoactivation (Coan & Allen, 2004), such that *greater* alpha power in one hemisphere (as compared to the other) indicates *lower* tonic cortical activity in the former (than in the latter). Greater left, relative to right, tonic activity in frontal regions is thought to reflect greater reward approach motivation, whereas greater right (relative to left) frontal activity is thought to reflect avoidance behaviours and disengagement (Davidson, 1992). These asymmetries are thought to arise from the biological processes underlying Gray's (1970) personality systems: the behavioural approach system (BAS), which is sensitive to reward and underlies motivation to approach rewards, and the behavioural inhibition system (BIS), which is sensitive to punishment or fear and can initiate avoidance behaviours (Davidson, 2004; Harmon-Jones, 2004). While a great deal of research has considered frontal alpha asymmetries in relation to psychometric measures of reward sensitivity, particularly Carver and White's (1994) BIS/BAS scales, relatively little work has examined alpha asymmetry in relation to reward related behaviour. Research that has considered reward related behaviour has tended to focus on approach behaviour (e.g. Hughes et al., 2015; Pizzagalli et al., 2005) and little work has sought to characterise loss aversion specifically.

1.4 EEG asymmetry and avoidance behaviour in infancy

The developmental literature on attachment has consistently linked frontal EEG asymmetries to inhibited / avoidance behaviours in the face of novel / threatening stimuli (see Gander & Bucheim, 2015 for a review). Calkins, Fox and Marshall (1996) observed greater right (compared to left) frontal activation in 9 month olds, which was associated with increased inhibited exploratory behaviour at 14 months in a group of infants classified as high negative affect, compared to their high positive affect peers. Similarly, Hane, Fox, Henderson and Marshall (2008) found that four-month-old infants prone to negative reactions were more likely to show avoidance behaviour and reduced approach behaviour in the face of a fearful stimulus at 9 months, which was accompanied by a pattern of greater right (relative to left) frontal EEG asymmetry. Extending this work, Buss et al. (2003) report a link between avoidant behaviours (fear and sadness), relative right asymmetry and higher levels of both basal and reactive cortisol in 6-month old infants in response to a negative affect task.

1.5 Loss aversion and resting state EEG asymmetries

Given the above research, a link between loss aversion, a putative avoidance behaviour, and right frontal alpha asymmetry would be expected. However, research findings in this area have been mixed. Some research has identified a predictive role for right (relative to left) PFC activity in individual risk taking behaviour. Specifically, Gianotti et al (2009) found that healthy participants with higher resting state activity in the right (compared to the left) PFC showed lower levels of risk averse behaviour on a gambling task. Aversion to risk is generally thought to arise as a result of loss aversion (Kobberling & Wakker, 2005). Similarly, Studer, Pedroni & Rieskamp (2013) report a relationship between increased right (relative to left) cortical hypoactivity and increased risk-taking behaviour, suggesting diminished loss aversion. Interestingly, they also highlight a relationship between increased BIS scores and decreased risk taking behaviour. Work by Schutter and van Honk (2005), in contrast, has examined the relationship between disadvantageous decision making on the Iowa Gambling Task and the ratio between frontal low-frequency oscillations (indicating cortical inactivity) and high-frequency oscillations (indicating cortical activity) during resting state. While higher values of the frontal EEG ratio were associated with more disadvantageous decision making, this effect was global and was found across both hemispheres. Additionally, the ratio of low- to high-frequency oscillations over *posterior* cortical regions was most significantly associated with disadvantageous decision making. Finally, Telpaz & Yechiam (2014) found that individuals with stronger left- than right-hemispheric frontal activity showed increased risk-taking on a mixed gambling task, relative to participants characterised by stronger right than left tonic activity.

1.6 Hypotheses

Given the mixed findings represented by the above studies and the links between frontal asymmetry and withdrawal behaviour and punishment avoidance, we sought to investigate the relationship between cortical asymmetry and loss aversion. We predicted that we would find an association between rightward asymmetry (i.e., stronger tonic activity in the right as compared to the left hemisphere) and greater loss aversion, as assessed by the loss aversion parameter λ. We further hypothesised that this effect would be most pronounced in frontal regions, given the neuropsychological and neuroscientific evidence supporting the role of the right PFC in avoidance behaviours. Given the existent inconsistent reports on the location of asymmetry indices, we also considered asymmetry values at central and posterior sites in relation to loss aversion.

2. Methods

2.1 Participants

N=41 healthy participants (23 female; mean age *M*=22.8 years, *SD*=4.33 years) volunteered their time in exchange for course credit. One participant was excluded due to excessive data loss during the EEG analysis, leaving a final *N*=40.

All participants were free of past or present neurological or psychiatric disorders. Data from the same participants have already been reported in Voigt et al. (2015). The study protocol complied with the Declaration of Helsinki and was approved by the local ethics committee of the Department of Psychology at the University of Bonn.

2.2 Electrophysiological recordings

Resting-state EEG was recorded from nine channels (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) with Ag/AgCl electrodes using a BrainProducts System (BrainProducts, Munich, Germany) that consisted of aV-Amp 16 amplifier and VisionRecorder software. AFz was used as a ground electrode. Two additional electrodes were placed on the outer left canthus (HEOG) and below the right eye (VEOG) to record eye movements. During recording the signal was referenced to the left mastoid (M1) and was re-referenced offline to Cz. Data were recorded with a sampling rate of 500 Hz and all electrode impedances were kept below 5 kΩ. During recording a Notch-Filter (50Hz) was applied. We recorded a total of four minutes of resting-state EEG. Participants alternated between eyes-open (20s) and closed (40s) to keep our procedure as close to Gianotti et al. (2009) as possible. However, eyes-open segments were heavily affected by eye motion artifacts, yielding unsatisfactory data. This was also reflected in a very low internal consistency of α = .5 between eyes-open and -closed segments. In-keeping with Gianotti et al. (2009) we thus decided to analyze eyes-closed segments only.

2.3 Data reduction and analysis

Preprocessing of the EEG data was carried out using BrainVision Analyzer V.1.05 (Brain Products GmbH, Munich, Germany). A 0.5–50Hz band pass filter was applied to the data. Data were then segmented into eyes-open and eyes-closed conditions. The data from the eyes closed conditions were combined (160s) and only recordings from these periods were analysed further (see Gianotti et al., 2009). Data were scored by eye and any obvious muscle artifacts were removed manually. No ocular artifact correction was necessary, given that the data used in the present analysis were only obtained from the eyes closed condition. Additional artifact rejection was carried out based on the criterion of amplitudes exceeding $\pm$200µV. All data were then segmented into 2s epochs with a 50% overlap, in-keeping with previous work considering frontal alpha asymmetry (e.g. Allen, Coan & Nazarian, 2004; Boksem et al., 2012; Hughes et al., 2015). Finally, a fast Fourier transform (FFT) with a 100% Hamming window was used to extract power spectral density (μV^2/Hz). Data were averaged for each EEG channel to produce a single power estimate for each channel. Spectral power in the alpha band (8–12.75Hz) was extracted for each participant from frontal (F3, F4), central (C3, C4) and posterior (P3, P4) sites. Alpha asymmetry in all three locations were considered, given the inconsistent findings from previous studies.

2.4 Right frontal asymmetry

Alpha power values from each of the six locations were log transformed to correct for positive skew. Note that we expected to find a link between loss aversion and

stronger right- relative to left-hemispheric cortical activation. Therefore, we computed asymmetry scores indicating greater left than right alpha power (i.e., stronger right than left cortical activity). This was done for all three recording locations (frontal: F3–F4; central: C3-C4; posterior: P3-P4).

2.5 Behavioural testing

Behavioural loss aversion was assessed following the procedure described by Tom et al. (2007) and used previously by our group (Voigt et al., 2015; Markett et al., 2016). We presented 256 mixed-gambles that offered a 50% chance to either win or lose a displayed amount of money. Potential gains ranged from 1.00 to 4.00 € with increments of 20 cents and potential losses ranged from 0.50 to 2.00 € with increments of 10 cents. All 256 possible combinations of gains and losses were administered in random order. The range of gains and losses were set to cover the typical range in which loss averse behaviour occurs.

On each trial, participants were asked to either accept or reject the gamble. Participants responded on a 4-point Likert scale ranging from "strongly reject", over "weakly reject", and "weakly accept" to "strongly accept". We used the scale to encourage deliberate answers from the participants. To determine gambling outcome and for our analysis, however, responses were collapsed into a binary "accept" vs. "reject" scheme.

No immediate feedback on gambling outcome was given during the experiment. Prior to the experiment, participants were informed that three of their gambles would be randomly selected and gambled by tossing a coin. Monetary gains and losses arising from these three gambles were either added to or subtracted from an initial endowment of 5.00 € that participants had received prior to the experiment. Thus, participants were aware prior to the experiment that their decision behaviour could lead to actual monetary gain or loss.

The 256 trials were spaced by an 8s inter-trial interval and grouped into five blocks. The inter-trial interval was set to allow for the parallel recording of electrodermal activity (not part of the present report). Between blocks, participants were given the chance to rest.

The individual loss aversion parameter λ served as main outcome variable. Individual λs were obtained by fitting a separate binary logistic regression model for each participant to predict the binary criterion "accept" vs. "reject" from the gambles' gains and losses. Loss aversion λ was then computed as the ratio of the beta weights for losses and gains ($\lambda = -\beta_{loss} / \beta_{gain}$). This ratio reflects the weighting of gains relative to losses and is commonly used to quantify dispositional loss aversion (Tom et al., 2007; Heeren et al., 2016; Markett et al., 2016).

2.6 Statistical analyses

To correct for slight positive skew, the loss aversion parameter λ was log transformed. The main hypotheses were tested using a series of Pearson correlations to assess the strength of relationships between loss aversion (log λ)

and alpha power at frontal, central and posterior sites. Post-hoc analysis of the significant relationships between loss aversion and central and posterior right-left asymmetry was carried out to determine the contribution of each hemisphere to the asymmetry scores. This was performed in line with the procedure introduced by Wheeler, Davidson & Tomarken (1993; see also Allen, Coan & Nazarian, 2004). Power at the electrodes of interest (i.e. central site: C3 and C4, and posterior site: P3 and P4) was residualised using a hierarchical regression model with the predictors: 1) average power across all electrode sites, and 2) power from the homologous electrode (i.e. P3 or P4 respectively). Resultant unstandardized residual values from P3 and P4 were then correlated with the loss aversion parameter (log λ). Rationale for these predictors is discussed in detail by Wheeler et al. (1993) and Allen et al. (2004), but can be briefly summarised as controlling for individual differences, such as scalp thickness and volume conducted activity from the homologous site, with the aim of isolating and retaining power from the approximate region of interest, e.g. the right posterior electrode, P4. Given previous research suggesting gender differences in hemispheric asymmetry (e.g. Baving, Laucht & Schmidt, 2002; Miller et al., 2002; but see also Thibodeau, Jorgensen & Kim, 2006), participants were divided into two groups based on their gender (females = 23) and Pearson's correlations were calculated separately for males and females to assess respective patterns of the relationships between loss aversion and hemispheric asymmetry at central and posterior sites.

3. Results

3.1 *Age and gender effects*

Neither age nor gender was associated with the loss aversion parameter λ (age: r = -.107, p = .512; gender: r = -.126, p = .440). The same holds for analyses using log λ (age: r = -.139, p = .393; gender: r = -.086, p = .600). Likewise, asymmetry scores across the three sites were not associated with gender (frontal: r = .025, p = .879; central: r = .174, p = .283; posterior: r = -.053, p = .744) or age (frontal: r = -.143, p = .379; central: r = .059, p = .717; posterior: r = .111, p = .496).

3.2 Behavioural data

The mean loss aversion score observed for this sample was 2.02 (SD = 1.11; λ = 2 reflects the aforementioned 2:1 ratio for loss aversion). The median was λ = 1.84. The mean of the log λ values was log λ = .578 (SD = .496).

3.3 Relationship between alpha asymmetry and behavioural loss aversion

A series of Pearson's correlations were carried out to assess the relationship between hemispheric asymmetry in the alpha band (scored so that higher values indicate stronger right- than left-hemispheric cortical activity) and behavioural loss aversion as quantified by the log-transformed parameter log λ. The relationship between asymmetry in the alpha band at frontal sites (M = .043, SD = .136) and log λ was non-significant (r = .103, p = .529). Unpredicted by our hypotheses, a significant relationship was observed between alpha asymmetry at central recording sites (M = .244, SD = .235) and log λ (r = .348, p = .028, 95% CI

[.040, .655]). Similarly, unpredicted by our hypotheses, a significant relationship was found between cortical asymmetry scores at posterior sites (M = .119, SD = .322) and log λ (r = .482, p = .002, 95% CI [.195, .770]). These relationships are depicted in Figures 1 and 2 below. Two outliers can be identified from these plots. Exclusion of these outliers made no major difference to the strength of the correlation relationships observed (central: r = .358, p = .028; posterior: r = .439, p = .006).

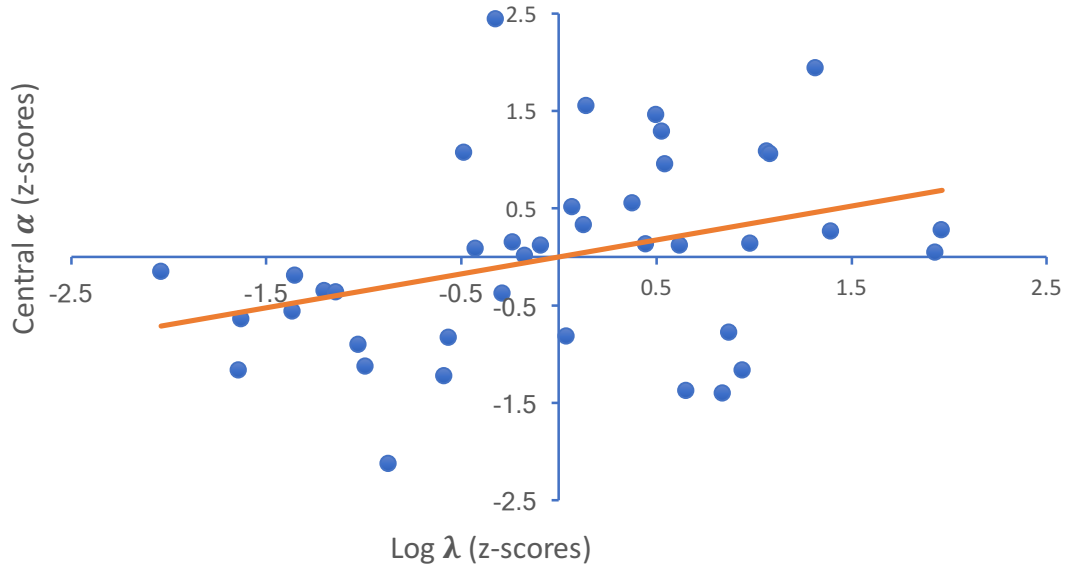

Figure 1: Correlational relationship between right-left asymmetry at central electrodes and log-transformed loss aversion parameter λ (including outliers).

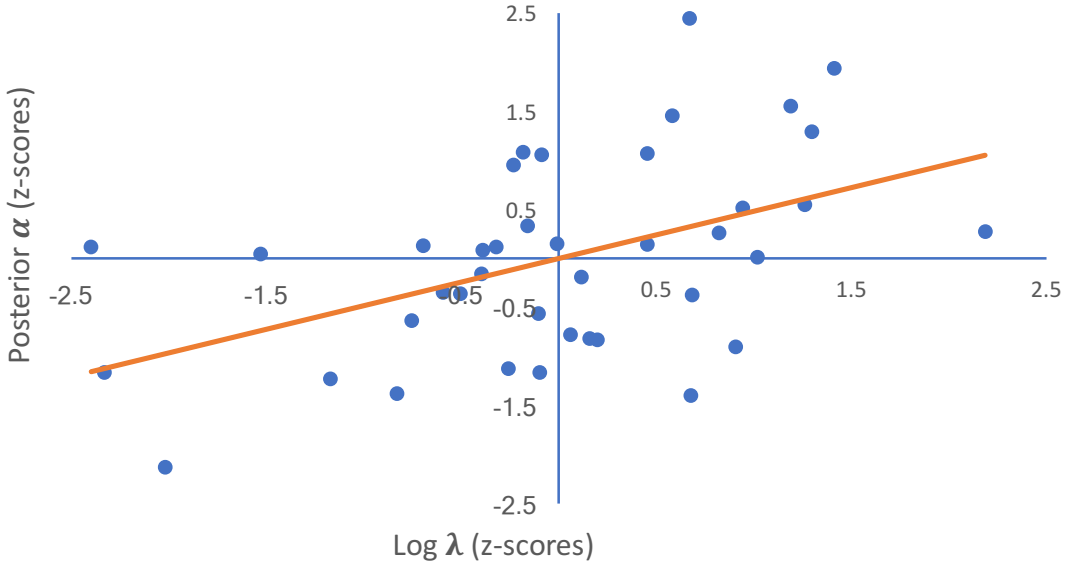

Figure 2: Correlational relationship between right-left asymmetry at posterior electrodes and log-transformed loss aversion parameter λ (including outliers).

Post-hoc Analyses

3.4 Respective right and left hemisphere contributions to alpha asymmetry

To parse the relative contributions of the right and left hemispheres to the asymmetry scores at central and posterior locations, a hierarchical regression model was created with two predictors: 1) Average power across all scalp-recorded electrodes, and 2) power from the homologous electrode site. Resultant unstandardized residual values for C3, C4, P3 and P4 were then correlated with the loss aversion. The results of these correlations are presented in table 1. For both central and posterior sites, a similar pattern of cortical activation can be observed as influencing the asymmetry score. Specifically, increased activation in the right hemisphere (i.e. decreased α power, as indicated by the negative sign) and decreased activation in the left hemisphere (i.e. increased α power, as indicated by the positive sign) are both significantly related to the loss aversion parameter log λ.

Table 1: Correlations between loss aversion (log λ) and the unstandardized residual α power indices at central and posterior left and right hemisphere electrodes

	Right Hemisphere		Left Hemisphere	
	C4	P4	C3	P3
log λ				
r	-.349	-.376	.333	.478
p	.028	.017	.036	.002
95% CI	[-.656, -.041]	[.024, .643]	[.189, .766]	[-.680, .072]

3.5 Loss aversion and asymmetry by gender

Participants were divided into two groups based on their gender to investigate whether the relationships between hemispheric asymmetry and log λ differed for males compared to females. For males, the Pearson correlation between log λ and posterior alpha asymmetry grew larger (r = .686, p = .002, 95% CI [.234, .891]), while the relationship between central asymmetry and log λ became non-significant (r = .229. p = .378). For females, this pattern was reversed, showing a non-significant relationship between alpha asymmetry at posterior regions (r = .335, p = .118) and a marginally stronger relationship between central asymmetry and log λ (r = .448, p = .032, 95% CI [.043, .872]). These relationships are depicted in figures 3 and 4.

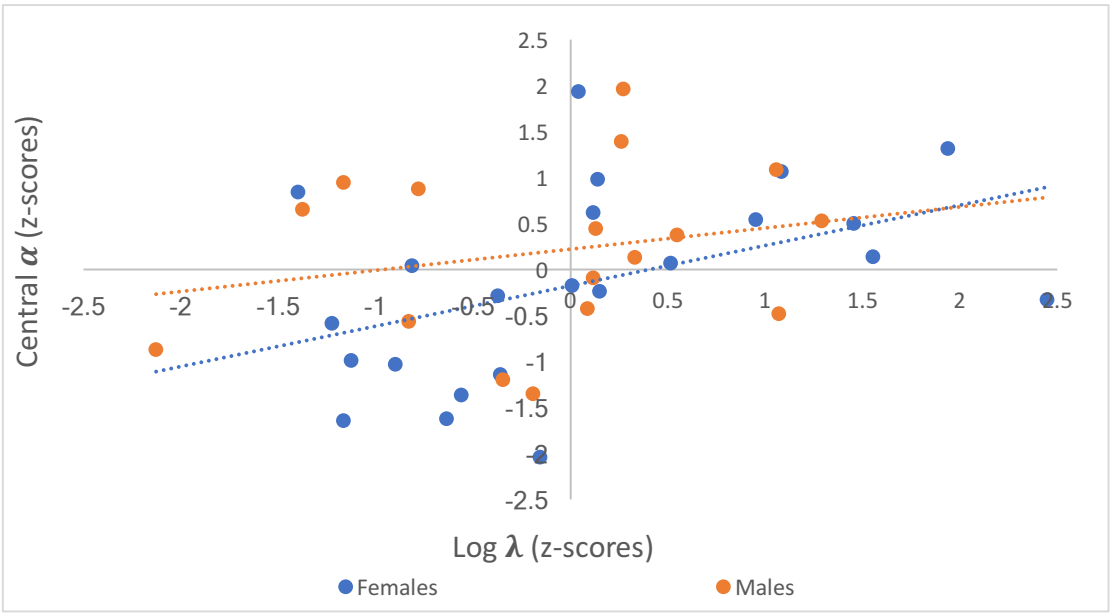

Figure 3: Correlational relationship between right-left asymmetry at central electrodes and log-transformed loss aversion parameter λ for males (red) and females (blue).

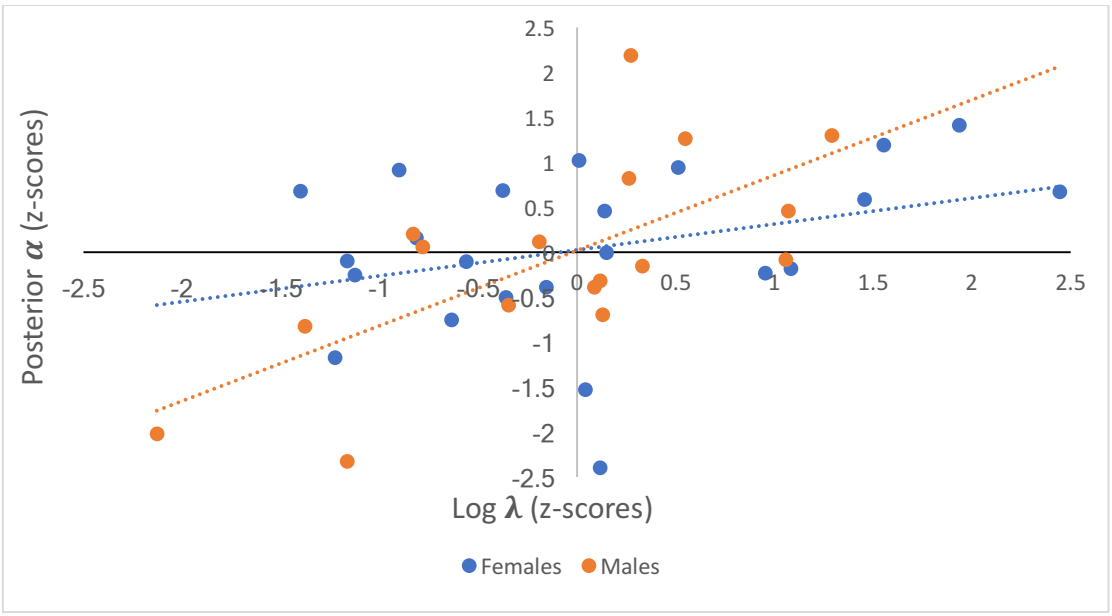

Figure 4: Correlational relationship between right-left asymmetry at posterior electrodes and log-transformed loss aversion parameter λ for males (red) and females (blue).

4. Discussion

We recorded resting state EEG activity from participants before they engaged in a mixed gambles task, designed to assess behavioural loss aversion. Behavioural loss aversion was associated with cortical asymmetry, as expected: stronger right- than left-hemispheric activation was associated with higher levels of loss

aversion. Interestingly, this effect was observed only for central (C3-C4) and posterior electrodes (P3–P4), which was not in line with our hypothesis. Thus, in the present study, participants with greater right (relative to left) tonic cortical activity in central and posterior regions showed greater behavioural loss aversion when undertaking gambles with a 50% chance of winning or losing money.

Our mean Lambda (λ) of 2.02 reflects previous findings (e.g., Haigh & List, 2005; Heeren et al., 2016; Johnson & Goldstein, 2003, Post et al., 2008; Tovar, 2009) and is in-keeping with the observation of Kahneman (2003) that, as individuals tend to be loss averse, they will only accept 50/50 gambles when the amount they stand to win exceeds that they stand to lose at a ratio of 2:1. The finding that loss averse behaviour is associated with greater right activity is also in-keeping with previous findings from patients with brain damage to the right hemisphere, who demonstrate decreased loss aversion in the form of more risky decisions on gambling tasks (e.g., Rahman et al., 2001; Clark et al., 2003; Tranel, Bechara & Denburg, 2002). This literature suggests the lateralisation of the right hemisphere in economic decision making (see also Gianotti et al., 2009; Knoch, Gianotti, Baumgartner, & Fehr, 2010; Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006) and that individual differences in the neural function of the right hemisphere may lead to variation in behavioural loss aversion.

While our findings are in keeping with the notion that lateralisation of the right hemisphere may underlie individual variation in behavioural loss aversion, the research attempting to characterise the neural bases of this variation is less convincing. EEG studies have attempted to broadly localise asymmetries in participants' resting state EEG recordings to frontal, central, or posterior sites. Resting state EEG has been found to be a relatively stable marker of behavioural approach and avoidance over a period of months to years (e.g., Brooker, Canen, Davidson & Goldsmith, 2017; Davidson, 2004; Jones, Field, Davalos & Pickens, 1997; Tomarken et al., 1992; Vuga et al., 2006). EEG research on behavioural loss aversion, a putative avoidance behaviour, is scarce and reports mixed findings both in terms of the oscillations studied and the locations in which the asymmetries are observed. Previous studies indicate a relationship between behavioural approach and increased left relative to right activity, as assessed via alpha-band oscillations in the PFC (e.g., Hughes et al., 2015; Pizzagalli et al., 2005). Moreover, TMS research by Knoch et al. (2006a) suggests a causal role for the right dorsolateral PFC in moderating risky decisions. A large body of developmental literature also associates avoidance behaviours with right (relative to left) frontal asymmetry in children (see Gander & Bucheim, 2015 for a review). Based upon these findings, we expected to observe a link between loss aversion and frontal alpha-band asymmetry. Somewhat surprisingly, we observed a robust association only at central and posterior recording sites, which could not be observed at frontal locations. This finding, though unpredicted, supports earlier work by Schutter and van Honk (2005), who found that the relative proportion of low-frequency oscillations at parietal sites was significantly associated with risky decision making.

Post-hoc analyses indicated a different pattern of hemispheric asymmetry for females compared to males. We observed a significant relationship between loss

aversion and alpha asymmetry for females at the right central recording site and for males at the posterior site. Sex-specific patterns of asymmetry have been reported in the literature considering individual differences in hemispheric asymmetries. Baving, Laucht & Schmidt (2002) report greater right than left frontal activation in a group of 8 to 11-year-old girls with anxiety compared to their male peers, who showed greater left than right activity. Miller et al. (2002) identified the same patterns in female and male adults with a history of childhood depression. These gender differences are not always clear-cut, however, and Kline, Allen & Schwartz (1998) report contrary results. Furthermore, Thibodeau, Jorgensen & Kim (2006) investigated gender as a moderator of frontal alpha EEG asymmetry and found no influence of gender on effect size. Given the inconsistencies in the literature, we refrain from speculating about possible sources of this variance, but encourage other researchers to be mindful of potential gender differences in future studies.

Finally, it should also be acknowledged that the research on frontal asymmetries and behavioural approach and avoidance is not always clear-cut. Several methodological issues have been identified in research in this area, including a lack of attention paid to whether different regions (frontal, central, posterior) are differentially involved in specific tasks or act as a function of individual differences (see Allen, Coan & Nazarian, 2004 and Hagemann, 2004 for a discussion). Additionally, a meta-analysis by Wacker, Chavanon & Stemmler (2010) suggests that the relationship between frontal asymmetries and indices of behavioural approach are much weaker and more inconsistent than is typically assumed. In addition to this problem, studies considering frontal asymmetries have not always reported the corresponding asymmetry values for central and posterior locations (Jesulola et al., 2015), making it difficult to confirm the specificity of these findings.

Several limitations from our own study must also be acknowledged. Firstly, many of the confidence intervals associated with the significant results in the present study are quite wide. Thus, we urge caution in extrapolating from these results and emphasise the need for future work to replicate these findings. Secondly, EEG data were obtained from only nine electrodes. While these electrodes represent the most frequently investigated sites in EEG asymmetry research, it does limit our ability to test the specificity of our findings to these locations. Thirdly, we collected a relatively small amount of resting state data: just 160s from four intervals in which participants alternated between keeping their eyes open and closed. Experimental procedures in this area typically report a recording of 8 minutes, in which participants alternate between keeping their eyes open or closed. However, good reliability (Chronbach's alpha of 0.80 – 0.90) has been reported for recordings of 4 minutes duration (Hagemann, Naumann, Becker, Maier & Bartussek, 1998). Finally, it should be noted that we only report frequencies extracted from the alpha band in the current study, as our hypotheses were restricted to this frequency band. Given findings associating avoidance behaviours with cortical asymmetry in other frequency bands (e.g., theta, delta, beta), additional research is required to investigate the specificity of each frequency band to individual differences in loss aversion specifically and approach/avoidance behaviours more generally.

5. Conclusion

Our results indicate that stronger right, relative to left, tonic activity in central and in posterior cortical regions is associated with loss averse behaviour. Post-hoc analyses indicate that this relationship is driven by a combination of increased right and decreased left hemispheric activation and that the relationship between hemispheric site and loss aversion differs for males and females. These results contribute to the crucial, but currently limited existent literature investigating the neural basis of loss aversion.

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Appendix B: Hierarchical regression models used to parse the relative contribution of each hemisphere to the hemispheric asymmetry score in section 3.2.7

Following a method proposed by Wheeler, Davidson & Tomarken (1993), we conducted a series of hierarchical regression models to enable us to parse the relative contributions of the right and left hemispheres to the asymmetry scores at central and posterior locations. Each regression model was created with two predictors: 1) Average power across all scalp-recorded electrodes, and 2) power from the homologous electrode site. Resultant unstandardized residual values for C3, C4, P3 and P4 were then correlated with the loss aversion. The results of these correlations are presented in table 1 of the main paper. Here we present relevant tables for the hierarchical regression models as a convenience for any researchers who may wish to replicate the process.

Hierarchical regression model to calculate residual power at P4

Model Summary

Model	R	R Square	Adjusted R Square	SE
1	.961[1]	.923	.921	.343
2	.971[2]	.943	.940	.298

[1] Constant, Average power all electrodes
[2] Constant, Average power all electrodes, P3

Coefficients

	B	SE B	β
Step 1			
Constant	.148	.098	
Average all electrodes	1.037	.049	.961*
Step 2			
Constant	-.024	.098	
Average all electrodes	.469	.161	.434*
P3	.561	.153	.546*

*Significant at p<.01

Hierarchical regression model to calculate residual power at P3

Model Summary

Model	R	R Square	Adjusted R Square	SE
1	.965[1]	.931	.929	.315
2	.974[2]	.950	.947	.274

[1] Constant, Average power all electrodes
[2] Constant, Average power all electrodes, P4

Coefficients

	B	SE B	β
Step 1			
Constant	.306	.090	
Average all electrodes	1.014	.045	.965*
Step 2			
Constant	.236	.081	
Average all electrodes	.522	.140	.497*
P4	.474	.129	.487*

*Significant at p<.01

Hierarchical regression model to calculate residual power at C4

Model Summary

Model	R	R Square	Adjusted R Square	SE
1	.944[1]	.891	.888	.365
2	.977[2]	.954	.951	.241

[1] Constant, Average power all electrodes
[2] Constant, Average power all electrodes, C3

Coefficients

	B	SE B	β
Step 1			
Constant	-.374	.105	
Average all electrodes	.913	.052	.944*
Step 2			
Constant	-.235	.072	
Average all electrodes	-.006	.134	-.006
C3	1.001	.141	.982*

*Significant at p<.001

Hierarchical regression model to calculate residual power at C3

Model Summary

Model	R	R Square	Adjusted R Square	SE
1	.967[1]	.935	.933	.277
2	.986[2]	.972	.971	.183

[1] Constant, Average power all electrodes
[2] Constant, Average power all electrodes, C4

Coefficients

	B	SE B	β
Step 1			
Constant	-.139	.079	
Average all electrodes	.918	.039	.967*
Step 2			
Constant	.077	.061	
Average all electrodes	.393	.079	.414*
C4	.575	.081	.586*

*Significant at p<.001

Appendix C: Full list of all 171 items used in the exploratory factor analysis of the GAME

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
When I'm doing well at something, I love to keep at it.	1	2	3	4	5
I prefer watching television to going out with other people.	1	2	3	4	5
When I see an opportunity for something I like I get excited right away.	1	2	3	4	5
I would enjoy a cup of tea or coffee or my favourite drink.	1	2	3	4	5
In many ways, I prefer the company of pets to the company of people.	1	2	3	4	5
I have a lot of fun.	1	2	3	4	5
If I see a chance to get something I want I move on it right away.	1	2	3	4	5
I feel lucky most of the time.	1	2	3	4	5
When I'm on my way to an amusement park, I can hardly wait to ride the rollercoasters.	1	2	3	4	5
Sex is the most intensely enjoyable thing in life.	1	2	3	4	5
Your work on a physical fitness program results in many compliments on how healthy and trim you are looking.	1	2	3	4	5
I will often do things for no other reason than that they might be fun.	1	2	3	4	5
I enjoy watching films about friendships or relationships with my friends.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
A good meal always tastes better when you eat it with someone you feel close to.	1	2	3	4	5
I crave excitement and new sensations.	1	2	3	4	5
I am not a joyful person.	1	2	3	4	5
When you leave the house wearing new and attractive clothes, you find it pleasurable when several people give you complements on how good you look.	1	2	3	4	5
A good soap lather when I'm bathing has sometimes soothed and refreshed me.	1	2	3	4	5
The beauty of sunsets is greatly overrated.	1	2	3	4	5
You are excited when someone you are sexually interested in takes a special interest in you.	1	2	3	4	5
I worry about my health, including physical problems such as aches and pains, or upset stomach or constipation.	1	2	3	4	5
I look forward to a lot of things in my life.	1	2	3	4	5
When I want something I usually go all-out to get it.	1	2	3	4	5
If I see a chance for something I want, I move on it right away.	1	2	3	4	5
I am usually content to just sit alone, thinking and daydreaming.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
You are excited to discover in the newspaper that your lottery ticket is worth $5000.	1	2	3	4	5
I get little pleasure from the physical activities I used to enjoy.	1	2	3	4	5
I have always had a number of favourite foods.	1	2	3	4	5
I have often found it hard to resist talking to a good friend, even when I have other things to do.	1	2	3	4	5
I excel in what I do.	1	2	3	4	5
I don't sleep well.	1	2	3	4	5
I really enjoy the feeling of a good yawn.	1	2	3	4	5
A hot cup of coffee or tea on a cold morning is very satisfying to me.	1	2	3	4	5
I have not lost interest in other people.	1	2	3	4	5
I would enjoy reading a book, magazine or newspaper.	1	2	3	4	5
I am disinterested in other people.	1	2	3	4	5
You are pleased to be skiing down a mountain very fast while still in good control of yourself.	1	2	3	4	5
When others try to tell me about their problems and hang-ups, I usually listen with interest and attention.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
You are pleased to find yourself at a lively party with many fascinating people.	1	2	3	4	5
You are excited to take off on a trip to China, scheduled to visit all the places you've heard and read about.	1	2	3	4	5
I have been fascinated with the dancing of flames in a fireplace.	1	2	3	4	5
You find it pleasurable to sit watching a beautiful sunset in an isolated, untouched part of the world.	1	2	3	4	5
I have always hated the feeling of exhaustion that comes from vigorous activity.	1	2	3	4	5
I have a low opinion of myself.	1	2	3	4	5
When things are going really good for my close friends, it makes me feel good too.	1	2	3	4	5
Although there are things that I enjoy doing by myself, I usually seem to have more fun when I do things with other people.	1	2	3	4	5
I am excited when a friend that I haven't seen in a while contacts me to make plans.	1	2	3	4	5
You are happy to reach full sexual climax with someone you love very much.	1	2	3	4	5
I get annoyed or irritated easily.	1	2	3	4	5
Trying new foods is something I have always enjoyed.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
You get satisfaction from coming to the end of a difficult work project that has taken much of your energy and many weeks of time.	1	2	3	4	5
I look forward to watching my favourite TV shows with my friends.	1	2	3	4	5
Sunbathing isn't really more fun than lying down indoors.	1	2	3	4	5
People often expect me to spend more time talking with them than I would like.	1	2	3	4	5
A car ride is much more enjoyable if someone is with me.	1	2	3	4	5
I have sometimes danced by myself just to feel my body move with the music.	1	2	3	4	5
My emotional responses seem very different from those of other people.	1	2	3	4	5
I enjoy it when a friend and I can discuss important things.	1	2	3	4	5
You enjoy listening to beautiful music in peaceful surroundings.	1	2	3	4	5
If I discover something new I like, I usually continue doing it for a while.	1	2	3	4	5
I enjoy going on group activities like attending sports events or concerts with my friends.	1	2	3	4	5
I've never cared much about the texture of food.	1	2	3	4	5
It has often felt good to massage my muscles when they are tired or sore.	1	2	3	4	5

I am not highly motivated to succeed.	1	2	3	4	5
My relationships with other people never get very intense.	1	2	3	4	5
Dancing, or the idea of it, has always seemed dull to me.	1	2	3	4	5
I would enjoy looking smart when I have made an effort with my appearance.	1	2	3	4	5
It's fun to sing with other people.	1	2	3	4	5
I would enjoy my favourite television or radio programme.	1	2	3	4	5
I am critical of myself for my weaknesses and mistakes.	1	2	3	4	5
Standing on a high place and looking out over the view is very exciting.	1	2	3	4	5
I enjoy joking and talking with a friend or co-worker.	1	2	3	4	5
I get little pleasure from interacting with a co-worker or classmate.	1	2	3	4	5
When I think of something tasty, like a chocolate chip cookie, I have to have one.	1	2	3	4	5
The colour that things are painted has seldom mattered to me.	1	2	3	4	5
When I go after something I use a "no holds barred" approach.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
A person's family is the most important thing in life.	1	2	3	4	5
I would enjoy a warm bath or refreshing shower.	1	2	3	4	5
I do just enough work to get by.	1	2	3	4	5
I have usually found lovemaking to be intensely pleasurable.	1	2	3	4	5
One food tastes as good as another to me.	1	2	3	4	5
I find that people too often assume that their daily activities and opinions will be interesting to me.	1	2	3	4	5
You are pleased when your supervisor gives you an unexpected merit or pay increase in recognition for outstanding work.	1	2	3	4	5
Sex is okay, but not as much fun as most people claim it is.	1	2	3	4	5
I'm much too independent to really get involved with other people.	1	2	3	4	5
I think that flying a kite is silly.	1	2	3	4	5
I have had very little desire to try new kinds of foods.	1	2	3	4	5
I no longer get excited the night before a fun event.	1	2	3	4	5
Playing with children is a real chore.	1	2	3	4	5
I have never found a thunderstorm exhilarating.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
It has always made me feel good when someone I care about reaches out to touch me.	1	2	3	4	5
I find it comforting to know I have friends who care about me.	1	2	3	4	5
I have often enjoyed receiving a strong, warm handshake.	1	2	3	4	5
The smell of freshly cut grass is enjoyable to me.	1	2	3	4	5
I never have the desire to take off my shoes and walk through a puddle barefoot.	1	2	3	4	5
Flowers aren't as beautiful as many people claim.	1	2	3	4	5
On hearing a good song, I have seldom wanted to sing along with it.	1	2	3	4	5
I am disappointed with myself.	1	2	3	4	5
When something exciting is coming up in my life, I really look forward to it.	1	2	3	4	5
I prefer hobbies and leisure activities that do not involve other people.	1	2	3	4	5
I enjoy looking at photographs of my friends and family.	1	2	3	4	5
I have often felt uncomfortable when my friends touch me.	1	2	3	4	5
Being with my friends makes me feel good.	1	2	3	4	5
When eating a favourite food, I have often tried to eat slowly to make it last longer.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
I've never cared to sunbathe; it just makes me hot.	1	2	3	4	5
I have no interest in having strong relationships with people.	1	2	3	4	5
I am disinterested in sex.	1	2	3	4	5
I never give up.	1	2	3	4	5
When I pass by flowers, I have often stopped to smell them.	1	2	3	4	5
I feel that my life lacks direction.	1	2	3	4	5
I love the sound of rain on the windows when I'm lying in my warm bed.	1	2	3	4	5
I would do anything to achieve my goals.	1	2	3	4	5
You are happy at completing a job that you find meaningful because of its immediate results.	1	2	3	4	5
I never wanted to go on any of the rides at an amusement park.	1	2	3	4	5
When I think about eating my favourite food, I can almost taste how good it is.	1	2	3	4	5
It's hard for me to find the time to do things such as get a haircut.	1	2	3	4	5
You feel good when someone calls on you for help during an emergency, and your help sees him/her through a difficult situation.	1	2	3	4	5
I have seldom enjoyed any kind of sexual experience.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
I am motivated to earn money.	1	2	3	4	5
People's daily activities and opinions are of no interest to me.	1	2	3	4	5
I put little time and effort into my work.	1	2	3	4	5
While raking leaves on a beautiful autumn day, you pause to watch some children playing in the leaf-piles.	1	2	3	4	5
I try to outdo others.	1	2	3	4	5
When I am successful at something, I keep doing it.	1	2	3	4	5
I would be able to enjoy my favourite meal.	1	2	3	4	5
I love it when people play with my hair.	1	2	3	4	5
I enjoy life.	1	2	3	4	5
I have a slow pace to my life.	1	2	3	4	5
The taste of food has always been important to me.	1	2	3	4	5
I like talking with others while waiting in a queue.	1	2	3	4	5
If given the choice, I would much rather be with others than be alone.	1	2	3	4	5
The warmth of an open fireplace hasn't especially soothed and calmed me.	1	2	3	4	5
I have very little affection for those who are close to me.	1	2	3	4	5
Making new friends isn't worth the energy it takes.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
You are proud when while fishing you feel a tug on your line and watch a 6-pound fish jump out of the water with your bait in its mouth.	1	2	3	4	5
After some vigorous physical exercise, you pause to catch your breath and relax your muscles.	1	2	3	4	5
The bright lights of a city are exciting to look at.	1	2	3	4	5
I continue until everything is perfect.	1	2	3	4	5
I would find pleasure in small things, e.g. a bright sunny day, a telephone call from a friend.	1	2	3	4	5
I like to make long distance phone calls to friends and relatives.	1	2	3	4	5
I get so excited the night before a major holiday I can hardly sleep.	1	2	3	4	5
My appetite is not very good.	1	2	3	4	5
I often hang around doing nothing.	1	2	3	4	5
Just being with friends can make me feel really good.	1	2	3	4	5
I am disinterested in listening to people tell me about their problems and hang-ups.	1	2	3	4	5
I am someone who goes all out.	1	2	3	4	5
You enjoy lying soaking in a warm bath.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
After a busy day, a slow walk has often felt relaxing.	1	2	3	4	5
I have always enjoyed looking at photographs of friends.	1	2	3	4	5
I appreciate being invited to hang out with people I know after school or work.	1	2	3	4	5
I want to be the very best.	1	2	3	4	5
I feel that nothing seems to make me feel good	1	2	3	4	5
I regularly shirk my duties.	1	2	3	4	5
When I am alone, I often resent people telephoning me or knocking on my door.	1	2	3	4	5
I do more than what's expected of me.	1	2	3	4	5
People who try to get to know me better usually give up after awhile.	1	2	3	4	5
When good things happen to me, it affects me strongly.	1	2	3	4	5
I often feel blue.	1	2	3	4	5
Although I know I should have affection for certain people, I don't really feel it.	1	2	3	4	5
I work too much.	1	2	3	4	5
When someone close to me is depressed, it brings me down also.	1	2	3	4	5
I imagine how much fun it would be to go on vacation with a friend or someone I love.	1	2	3	4	5
I don't enjoy the things I used to.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
I find it difficult to get down to work.	1	2	3	4	5
I sometimes become deeply attached to people I spend a lot of time with.	1	2	3	4	5
I often try to lead others.	1	2	3	4	5
I'm always willing to try something new if I think it will be fun.	1	2	3	4	5
When I'm doing well at something I love to keep at it.	1	2	3	4	5
The sounds of a parade have never excited me.	1	2	3	4	5
I have seldom cared to sing in the shower.	1	2	3	4	5
I feel I may be being punished.	1	2	3	4	5
You lie basking in the sun on a relaxed weekend.	1	2	3	4	5
You are happy when a group of your neighbours selects you to receive an award for your work in the community.	1	2	3	4	5
How I dress is important to me.	1	2	3	4	5
It made me sad to see all my high school friends go their separate ways when high school was over.	1	2	3	4	5
Beautiful scenery has been a great delight to me.	1	2	3	4	5
I have trouble getting interested in things.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
I attach very little importance to having close friends.	1	2	3	4	5
I like it when people call or text me to say hi.	1	2	3	4	5
I have always found organ music dull and unexciting.	1	2	3	4	5
The first winter snowfall has often looked pretty to me.	1	2	3	4	5
I try to surpass others' accomplishments.	1	2	3	4	5
I enjoy taking a deep breath of fresh air when I walk outside.	1	2	3	4	5
I would prefer to live amongst people than all alone in a cabin in the woods.	1	2	3	4	5
I appreciate the beauty of a fresh snowfall.	1	2	3	4	5
I feel pleased and gratified as I learn more and more about the emotional life of my friends.	1	2	3	4	5
I would get pleasure from helping others.	1	2	3	4	5
There just are not many things that I have ever really enjoyed doing.	1	2	3	4	5
I go out of my way to get things I want.	1	2	3	4	5
I put off making decisions.	1	2	3	4	5
I have little interest in watching the types of movies I used to enjoy.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
I don't like my friends.	1	2	3	4	5
I don't really look forward to family get-togethers or gatherings.	1	2	3	4	5
I would be able to enjoy a beautiful landscape or view.	1	2	3	4	5
I never had really close friends in high school.	1	2	3	4	5
I do a lot in my spare time.	1	2	3	4	5
I look forward to seeing people when I'm on my way to a party or get-together.	1	2	3	4	5
On seeing a soft, thick carpet, I have sometimes had the impulse to take off my shoes and walk barefoot on it.	1	2	3	4	5
I don't care about my job performance.	1	2	3	4	5
I have thoughts of killing myself.	1	2	3	4	5
Having close friends is not as important as many people say.	1	2	3	4	5
I radiate joy.	1	2	3	4	5
People sometimes think that I am shy when I really just want to be left alone.	1	2	3	4	5
I work hard.	1	2	3	4	5
After much concentration and hard work you are happy when you finally master a new skill on your own.	1	2	3	4	5

	Very False for me	Moderately False for me	Neither False nor True for me	Moderately True for me	Very True for me
I have often enjoyed the feel of silk, velvet, or fur.	1	2	3	4	5
When something good happens to me, I can't wait to share the news with others.	1	2	3	4	5
I often act on the spur of the moment.	1	2	3	4	5
When I move to a new city, I feel a strong need to make new friends.	1	2	3	4	5
It takes extra effort to get started at doing something.	1	2	3	4	5
I am an energetic person.	1	2	3	4	5
I turn plans into action.	1	2	3	4	5
The sound of music has often thrilled me.	1	2	3	4	5
I have not lost interest in my favourite activities.	1	2	3	4	5
There are few things more tiring than to have a long, personal discussion with someone.	1	2	3	4	5
I have often found walks to be relaxing and enjoyable.	1	2	3	4	5
You are happy when someone who makes you feel loved wraps you in their arms and holds you close.	1	2	3	4	5
When I have seen a statue, I have had the urge to reach out and touch it.	1	2	3	4	5
You find it pleasurable to spend a slow and gentle period of time in sexual foreplay with someone you love.	1	2	3	4	5
I want to be in charge.	1	2	3	4	5

It is pleasurable when Someone gently begins to scratch your back.	1	2	3	4	5
When I'm feeling a little sad, singing has often made me feel happier.	1	2	3	4	5
I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread.	1	2	3	4	5
I like playing with and petting soft little kittens or puppies.	1	2	3	4	5

Appendix D: A list of the items from the 40-item revised version of the GAME

Item number	Subscale	Statement
1	IA	I have no interest in having strong relationships with other people
2	NE	I often feel blue
3	SP	I have often enjoyed the feeling of silk, velvet or fur
4	D	I crave excitement and new sensations
5	IA	Having close friends is not as important as many people say
6	NE	I am disappointed with myself
7	SP	I have been fascinated with the dancing of flames in a fireplace
8	D	I want to be the very best
9	IA	I attach very little importance to having close friends
10	NE	I have a low opinion of myself
11	SP	On seeing a soft, thick carpet, I have sometimes had the impulse to take off my shoes and walk barefoot on it
12	D	I get so excited the night before a fun event I can hardly sleep
13	IA	Making new friends isn't worth the energy it takes
14	NE	I feel that my life lacks direction
15	SP	The smell of freshly cut grass is enjoyable to me
16	IA	I'm much too independent to really get involved with other people
17	NE	I am critical of myself for my weaknesses and mistakes
18	SP	When I have seen a statue I have had the urge to reach out and touch it
19	D	How I dress is important to me
20	IA	I am disinterested in other people
21	NE	I don't enjoy the things I used to
22	SP	I really enjoy the feeling of a good yawn
23	D	I often act on the spur of the moment
24	IA	Other people's daily activities and opinions are of no interest to me
25	NE	I find it difficult to get down to work
26	SP	I have never had the desire to take my shoes off and walk through a puddle barefoot
27	D	When I'm on my way to an amusement park I can hardly wait to ride the rollercoasters
28	IA	There are few things more tiring than to have a long personal conversation with someone
29	NE	It takes extra effort to get started at doing something
30	SP	I have sometimes danced by myself just to feel my body move with the music
31	IA	I have often felt uncomfortable when my friends reach out to touch me
32	NE	I put off making decisions
33	IA	I don't really look forward to family get-togethers or gatherings
34	NE	I don't sleep well

35	IA	When I am alone I often resent people telephoning or texting me or knocking on my door
36	NE	I get annoyed or irritated easily
37	IA	I never really had close friends in high school
38	IA	My relationships with other people never get very intense
39	NE	I worry about my health, including physical problems such as aches and pains or upset stomach and constipation
40	IA	I prefer watching television to going out with other people

Appendix E: A list of the items dropped from the 50-item GAME

	Subscale	Item
1	D	You are pleased to be skiing down a mountain very fast while still in good control of yourself
2	D	I often try to lead others
3	IA	I find playing with children a real chore
4	NE	I have not lost interest in my favourite activities
5	NE	I have little interest in watching the types of movies I used to enjoy
6	SP	When I'm feeling a little sad, singing has often made me feel happier
7	SP	If I discover something new I like, I usually continue doing it for a while
8	SP	After a busy day, a slow walk has often felt relaxing
9	SP	It is pleasurable when someone gently begins to scratch your back
10	SP	When eating a favourite food, I have often tried to eat slowly to make it last longer