University of Reading

Anhedonia in Depression and the Case for Refining its Treatment: Insights from Examining the Neural Effects of Catecholaminergic Antidepressants

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Declaration

I confirm that this is my own work and the use of all material from other sources has been properly and fully acknowledged. In paper one, students assisted with data collection (Jess Bowles, Natasha Girling, Aran O'Doherty, Chelsea Owens, Ellen Partridge, Darcie Patten, Reilly Windsor-Daly and Emma Wylde). Further, I had begun data collection (7 participants) for paper two, during my MSc, prior to the start of my PhD.

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The research presented in papers 1-3 has been reported in articles that are published or in preparation for submission.

Dean, Z., Horndasch, S., Giannopoulos, P., & McCabe, C. (2016). Enhanced neural response to anticipation, effort and consummation of reward and aversion during bupropion treatment. *Psychological medicine, 46*(11), 2263-2274.

Dean, Z., & McCabe, C. (in preparation). Impaired Anticipatory Pleasure in Individuals with High Symptoms of Depression during a Progressive Ratio Effort task

Dean, Z., Antonesei, A., Anand, S.P., Butt, M., & McCabe, C. (in preparation). Increased Neural Response during the Anticipation and Effort to Avoid Aversion, but not Reward, Following Agomelatine Treatment

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1. Abstract

Anhedonia, clinically referred to as the loss of interest and/or pleasure, is a core symptom of Major Depressive Disorder (MDD). Although this criterion acknowledges impairments in motivational and consummatory domains, it is unclear how each aspect contributes to MDD. Examining this may assist with the development of more effective treatments, which is essential given that selective serotonin reuptake inhibitors (SSRIs) are ineffective at treating anhedonia. Intriguingly, it has been proposed that catecholaminergic antidepressants might be more suitable treatments for anhedonia in MDD. However, few empirical studies have been conducted in humans to examine this notion.

Three studies are included in this thesis. The first study investigated what aspects of reward processing are dysfunctional in individuals with high depression symptoms (HDS), using a novel progressive ratio task and explicit measures of wanting, anticipated pleasure, liking and intensity. We identified that individuals with HDS have deficits in accurately anticipating pleasure and a subset of HDS volunteers underestimate their performance. Interestingly, we did not observe impairments in experiencing pleasure to, or expending effort for, a pleasant taste. Our results not only contribute to the understanding of what reward-related aspects are impaired in individuals experiencing HDS, but they also have important methodological implications regarding how anhedonia is researched.

Studies two and three were the first to examine how two catecholaminergic antidepressants, bupropion and agomelatine, affect reward and aversion anticipation, effort and consummation in the healthy human brain. We found that bupropion increased brain activity during both reward *and* aversion processing, and that agomelatine enhanced neural activity during aversion processing. Our findings may help explain why catecholaminergic antidepressants might be more effective treatments for anhedonia and emotional blunting, compared to SSRIs. Taken together, this body of work provides valuable insight into the prospect of developing more personalised treatments for MDD, based on symptoms as opposed to diagnosis alone.

2. Introduction

2.1. Anhedonia in Major Depressive Disorder

Major Depressive Disorder (MDD) is one of the most common and burdensome mental health conditions in Europe, affecting, an estimated, 30.3 million people (Wittchen et al., 2011). MDD is associated with various adversities that impact everyday functioning and quality of life, extending over occupational (e.g. performance, discrimination and unemployment), social (e.g. stigmatisation, poor interpersonal relationships and poor social skills) and physical (e.g. fatigue, cardiovascular problems and suicide) domains (Birnbaum et al., 2010; Brouwers et al., 2016; Kessler, 2012; Kronmüller et al., 2011; Kupferberg, Bicks, & Hasler, 2016; Salomon, Clift, Karlsdóttir, & Rottenberg, 2009; Sokero et al., 2006) . In addition to the debilitating effects associated with MDD on an individual, it also puts a strain on families and has a large financial impact on society (Andlin-Sobocki, Jönsson, Wittchen, & Olesen, 2005; Birnbaum et al., 2010; Van Wijngaarden, Schene, & Koeter, 2004). As a result, it is imperative that research is conducted in order to improve our understanding of MDD, its causes and treatment.

A clinical diagnosis of MDD requires the presence of at least one of two core symptoms (low mood and anhedonia), in addition to a further five symptoms involving distortions to sleep, weight, motor functioning, energy levels, concentration or decisiveness, as well as feelings of worthlessness or guilt and suicidal ideation (American Psychiatric Association, 2013). Defined as the loss of interest or pleasure, anhedonia is a deficit in reward processing (American Psychiatric Association, 2013). Improving our understanding of anhedonia is particularly important as it has been shown to predict depression severity, depression-free days and remission (McMakin et al., 2012; Vrieze et al., 2014). Further, anhedonia has detrimental effects on patients' quality of life, due to its association with social withdrawal, social impairment, rumination and suicidal ideation (Ballard et al., 2017; Buckner, Joiner, Pettit, Lewinsohn, & Schmidt, 2008; Vinckier, Gourion, & Mouchabac, 2017). Whilst the prevalence of anhedonia in MDD is unknown, study demographics report that 70-86% of samples experience anhedonia, suggesting that it is highly prevalent (Buckner et al., 2008; Llorca & Gourion, 2015; Moayedoddin et al., 2013).

By clinical definition, the term anhedonia takes into account impairments in both reward motivation ("loss of interest") and reward liking ("loss of pleasure") (Argyropoulos & Nutt, 2013; Thomsen, Whybrow, & Kringelbach, 2015). Despite this, 'anhedonia' is often flippantly used to refer to reward-related deficits generally. To address this issue, it has recently been proposed that the terms 'motivational anhedonia' and 'consummatory anhedonia' are used, to clearly dissociate between a reduced drive to seek rewards and a reduced ability to experience pleasure, respectively (Treadway & Zald, 2011). Unfortunately, few experimental paradigms attempt to measure multiple reward dimensions within the same task, and those that do often fail to adequately separate these dimensions. As a result, it remains to be fully elucidated how the different reward components relate to MDD.

2.1.1. Consummatory Anhedonia in Major Depressive Disorder

Reward 'liking' in MDD is predominately measured via two self-report methods 1) questionnaires asking volunteers to rate how much pleasure would be, or has been, experienced in response to a given event (e.g. "I would enjoy a cup of tea or coffee or my favourite drink", from the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995)) and 2) delivering a pleasurable stimulus (e.g. a pleasant image, taste or smell) and asking volunteers to rate how much they 'like' the stimulus (Thomsen, 2015; Thomsen et al., 2015).

In support of consummatory anhedonia in MDD, numerous studies have found that patients with MDD and individuals with high symptoms of depression (HDS) report greater levels of consummatory anhedonia via questionnaires, compared to healthy controls (Berlin, Givry-Steiner, Lecrubier, & Puech, 1998; Sherdell, Waugh, & Gotlib, 2012; Treadway, Bossaller, Shelton, & Zald, 2012; Ubl et al., 2015; Yang et al., 2014). However, there is less support for consummatory anhedonia in MDD from studies that measure in-the-moment experiences of pleasure after delivering pleasant stimuli. For instance, although there are some reports of people with MDD experiencing less pleasure

when viewing positive images and film clips (Dunn, Dalgleish, Lawrence, Cusack, & Ogilvie, 2004a, 2004b; Kaviani et al., 2004), there is an overwhelming amount of research demonstrating that people with MDD report liking a variety of odours, tastes, positive images and humorous cartoons, to the same extent as healthy controls (Arrondo et al., 2015; Berlin et al., 1998; Clepce, Gossler, Reich, Kornhuber, & Thuerauf, 2010; Dichter, Smoski, Kampov-Polevoy, Gallop, & Garbutt, 2010; Dichter, Tomarken, Shelton, & Sutton, 2004; Forbes, Miller, Cohn, Fox, & Kovacs, 2005; Sherdell et al., 2012; Swiecicki et al., 2009). In fact, a recent review suggests that there is more behavioural evidence opposing a hedonic deficit in MDD, than there is in favour of it (Thomsen et al., 2015).

Interestingly, one study even found reports of reduced consummatory pleasure via a questionnaire, yet intact pleasure ratings to humorous stimuli, relative to healthy controls, within the *same* MDD sample (Sherdell et al., 2012). Given that discrepant reports of consummatory anhedonia were found within the *same* group of MDD participants, this eliminates the possibility that the inconsistent responses were due to heterogeneous sampling. Rather, it is intriguing to consider that questionnaires which aim to measure consummatory anhedonia may actually be capturing an inability to accurately predict how much pleasure would be experienced in response to a given pleasurable event (anticipatory anhedonia). This is since questionnaires, such as the SHAPS (Snaith et al., 1995), require volunteers to *imagine* how much pleasure would be obtained in a particular situation, whereas pleasure ratings collected immediately after reward delivery might more accurately measure *experienced* pleasure. Consistent with this suggestion, people with HDS and MDD report greater anticipatory anhedonia, compared to healthy controls, via questionnaires (Sherdell et al., 2012; Yang et al., 2014). Moreover, individuals with MDD report feeling less happy/excited prior to receiving a reward, which may indirectly indicate signs of anticipatory anhedonia (McFarland & Klein, 2009). Unfortunately, only a couple of studies have experimentally compared in-the-moment ratings of anticipated pleasure with experienced pleasure to a given reward (Chentsova-Dutton & Hanley, 2010; Wu et al., 2017). One naturalistic study collected ratings of anticipated and experienced pleasure in response to daily activities. They revealed that individuals with MDD anticipate experiencing less pleasure than healthy controls (Wu et al., 2017). However, this study also found that people with MDD *experienced* less pleasure

compared to healthy controls, suggesting that their prediction of reduced pleasure was accurate (Wu et al., 2017). However, given the lack of empirical investigation, further exploration is warranted using designs whereby the reward is identical for both the clinical and comparison groups and when anticipated and experienced pleasure is measured within close proximity of reward delivery.

Consummatory anhedonia has also been examined using more implicit measures than self-reports, such as through videoing facial expressions and collecting electromyography recordings to pleasant stimuli. Indeed, some studies find that people with HDS and a MDD diagnosis display less frequent and less intense emotional facial reactions to pleasant images, film clips and monetary rewards (Franzen & Brinkmann, 2016; Renneberg, Heyn, Gebhard, & Bachmann, 2005; Sloan, Bradley, Dimoulas, & Lang, 2002; Sloan, Strauss, & Wisner, 2001). This suggests that individuals with HDS and MDD may have reduced responsiveness to rewards, which may, in turn, signify reduced pleasure. However, the validity of measuring hedonic experience through facial responsiveness is unclear, especially since it has been demonstrated that individuals with MDD are more likely to supress smiles to positive stimuli (Reed, Sayette, & Cohn, 2007). In addition to this, some studies have not found differences between healthy controls and MDD patients in their facial expressions, heart rate or skin conductance reactivity to positive film clips (Gruber, Oveis, Keltner, & Johnson, 2011; Rottenberg, Gross, & Gotlib, 2005; Rottenberg, Kasch, Gross, & Gotlib, 2002). Consequently, it is unclear from these studies whether there are impairments in reward responsiveness and if this directly maps onto hedonic experience.

Consummatory anhedonia may also be suggested from impaired performance on probabilistic reward tasks. During these tasks, volunteers are asked to indicate whether a shorter or longer line, of 1.5mm difference, has been presented. Volunteers are rewarded three times more frequently for correctly identifying one line, than correctly identifying the other line. Whereas healthy controls develop a response bias, whereby they are more likely to *incorrectly* report seeing the more rewarded stimulus, individuals with HDS and a MDD diagnosis fail to develop this reward bias (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Pizzagalli, Jahn, & O'Shea, 2005). It is possible that individuals with

depressive symptoms fail to develop a reward-bias due to reduced reward responsiveness, which may suggest reduced reward liking. However, as mentioned above, reduced reward responsiveness may not directly translate to the experience of pleasure. Further, it is possible that the absence of a reward-bias could be due to impaired reward learning. This is especially possible, given that performance is only impaired on trials following unexpected outcomes i.e. when volunteers are not rewarded for correctly identifying the more rewarded stimulus or are rewarded for correctly identifying the less rewarded stimulus. Therefore, rather than suggesting consummatory anhedonia, impaired reward biases may suggest impairments in using reinforcement history to guide behaviour.

Neuroimaging techniques have also been used to investigate hedonic processing and, beneficially, bypass explicit subjective reports. For instance, functional magnetic resonance imaging (fMRI) is an indirect measure of neuronal activity, that can be used to compare brain activity between individuals experiencing HDS and healthy controls to pleasant stimuli (consummatory phase). Reduced brain activity to pleasant stimuli has been reported in MDD, in regions such as the ventral striatum (including nucleus accumbens (NAcc) caudate and putamen), insula and medial prefrontal cortex (mPFC) (Epstein et al., 2006; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; Pizzagalli et al., 2009). Whilst this suggests that there is abnormal brain activity during reward consummation, it is difficult to establish whether this directly translates to deficits in experienced pleasure. For instance, in addition to capturing brain activity related to reward liking, fMRI measures during consummatory phases are likely to also include neural activity linked to saliency. Nevertheless, activity in the ventral striatum when viewing positive words has been found to correlate with anhedonia, potentially suggesting that activity in the ventral striatum is related to reward liking (Epstein et al., 2006). However, this study measured anhedonia using a single item on a depression questionnaire, which did not separate between motivational or consummatory anhedonia. Moreover, positive words may not be an adequate measure of reward consummation. Additionally, other studies have failed to replicate a relationship between NAcc activity to pleasant stimuli and anhedonia scores (Pizzagalli et al., 2009). Finally, there are other studies within the literature that do not observe differences in neural activity between healthy controls and MDD patients, and some studies that only report aberrant activity in regions that are unlikely to be related to the experience of pleasure (e.g. occipital regions)

(Smoski, Rittenberg, & Dichter, 2011; Stoy et al., 2012; Ubl et al., 2015). Taken together, although there is some evidence to suggest that people with MDD have abnormal neural activity to pleasant stimuli, this may not be a pure measure of consummatory anhedonia.

2.1.2. Motivational Anhedonia in Major Depressive Disorder

Compared to reward liking, less research has examined the motivational ("loss of interest") construct of anhedonia in MDD. Motivational anhedonia is an incredibly complex symptom that could arise from a number of potential deficits. For example, reduced reward wanting and impairments in effectively integrating information to compute whether the benefits of a reward outweigh the costs of obtaining it (cost-benefit analysis), are some of the reasons why motivation might be reduced (Nunes, Randall, Podurgiel, Correa, & Salamone, 2013; Treadway & Zald, 2011).

Although it is difficult to distinguish between the different possible reasons *why* reward motivation might be impaired, some studies have attempted to specifically examine wanting in depression. One study explicitly measured whether reward 'wanting' was impaired in adolescents with HDS, by asking them to rate how much they 'wanted' a pleasant taste (Rzepa, Fisk, & McCabe, 2017). They found that adolescents with HDS rated wanting a pleasant taste to the same extent as healthy controls, suggesting that wanting is intact. However, other studies using more implicit measures have found evidence to suggest that reward wanting is impaired. For instance, some studies have examined heart rate whilst participants perform a cognitive task, in the attempt to obtain a monetary reward. Such studies have found that, unlike healthy volunteers whose heart rate increases with increasing reward magnitude, individuals with HDS have reduced heart rate reactivity, which remains consistent across reward incentives (Brinkmann & Franzen, 2013; Franzen & Brinkmann, 2015). In favour of motivational anhedonia, the authors suggest that their results indicate reduced wanting when anticipating monetary reward. However, blunted cardiovascular responses whilst working to obtain rewards of increasing value, may also signify impairments in other reward-related aspects. For instance, it may capture an inability to discriminate between different reward magnitudes

or anticipate pleasure. Consistent with the latter, heart rate reactivity has been found to be predicted by, not only, self-reported motivation to obtain the reward, but also by anticipatory pleasure (Franzen & Brinkmann, 2016). Consequently, although individuals with HDS have blunted cardiovascular responses during reward-related cognitive tasks, this may suggest impairments in other reward domains in addition to motivational anhedonia.

In the past decade, studies have begun to examine motivational anhedonia by examining how much effort volunteers are willing to invest in order to obtain reward (reward-related effort expenditure). Beneficially, this is similar to how reward motivation is measured in rodents, allowing for more direct comparisons between rodent and human experiments (Thomsen, 2015). Arguably, as discussed further below, these tasks may, more specifically, measure the ability to compute a cost-benefit analysis, as opposed to reward wanting per se (Treadway, Bossaller, et al., 2012; Treadway & Zald, 2011). To date, there are only four studies that have examined reward-related effort expenditure in individuals with MDD and two using samples that may be at 'elevated-risk' of MDD. All but two of these studies used the Effort-Expenditure for Rewards Task (EEfRT), which aims to measure effort-based decision making in the context of monetary reward (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). Participants are presented on a trial-by-trial basis with the choice between a high-effort/high-reward (HE/HR) and a low-effort/low-reward (LE/LR) option. Although modified versions exist, LE/LR trials typically require 30 key presses using the dominant finger within 7seconds, whereas HE/HR selections require 100 key presses in 21 seconds using the little finger. Successful completion of LE/LR trials could result in a fixed reward of $1, whereas successful completion of the HE/HR trials could result in a reward between $1.24 and $4.30. However, the reward is not always guaranteed and, thus, the probability of receiving a monetary reward after successful completion is presented during choice-selection (12%, 50% or 88%). The task terminates after twenty minutes and the number of HE/HR selections during the first 50 trials are analysed, with fewer HE/HR selections suggesting reduced reward motivation (Treadway et al., 2009).

In favour of motivational anhedonia in individuals at 'elevated risk' of MDD, it has been found that self-reports of anhedonia, via a questionnaire, predicts fewer HE/HR sections (Treadway et al., 2009). Additionally, individuals with HDS make fewer HE/HR choices compared to healthy controls (Yang et al., 2014). More specifically, both greater anhedonia and depression symptoms separately predicted fewer HE/HR selections when the reward magnitude was high and the probability of receiving the reward was ambiguous (i.e. 50% and not 12% or 88%). This suggests that anhedonia and depression symptoms negatively impact how much effort is invested in order to obtain a reward, particularly when the reward is large and the probability of being rewarded for successful completion is uncertain. Moreover, questionnaire scores of anticipatory, but not consummatory, anhedonia predicted fewer overall HE/HR selections (Yang et al., 2014). This may suggest that deficits in anticipating, but not experiencing, pleasure might be associated with reduced reward-related effort expenditure in individuals with HDS.

Similar to individuals with HDS, it has been indicated that MDD patients make fewer HE/HR selections on the EFfRT, compared to healthy controls (Treadway, Bossaller, et al., 2012; Yang et al., 2014). Interestingly, unlike individuals at 'elevated risk' of MDD, whose reduction in HE/HR selections was predicted by anticipatory anhedonia, decreases in HE/HR selections in MDD patients were predicted by anticipatory *and* consummatory anhedonia (Yang et al., 2014). This may suggest that, whereas deficits in anticipating pleasure is related to reduced reward-related effort expenditure in both 'at risk' and MDD samples, deficits in consummatory anhedonia may only be related to reward-related effort expenditure when symptoms become clinically relevant. Further, similar to individuals at 'elevated risk' of MDD, individuals with MDD made fewer HE/HR choices when the reward was large and the probability of attaining the reward was ambiguous. Interestingly, however, individuals with MDD also invested less effort when the reward magnitude was large and the probability of being rewarded was high (80%). This may suggest that deficits in reward-related effort expenditure may extend beyond ambiguous contexts, to likely rewarded events, when depression symptoms become clinically relevant.

Taken together, studies using the EEfRT suggest that reward motivation is impaired in individuals with HDS and MDD patients. However, as mentioned above, reduced reward-related effort expenditure may not represent impairments in how much a reward is wanted, *per se*. Instead, as discussed further in section 2.2.3, it may, for instance, signify deficits in overcoming the costs of effort (Nunes, Randall, Podurgiel, et al., 2013). Importantly, the creators of the EEfRT discuss this in a review paper and suggest that impairments in their task may be related to an inability to compute cost-benefit analyses (Treadway, Bossaller, et al., 2012; Treadway & Zald, 2011). More specifically, they suggest that individuals with HDS may either overestimate the costs of obtaining rewards and underestimate the benefits of rewards, or have impairments in integrating information to make the computation. This, in turn, impairs their ability to make optimal effort-based decisions in the context of rewards (Treadway, Bossaller, et al., 2012; Treadway & Zald, 2011).

Importantly, although it is undeniable that the computation of cost-benefit analyses contributes towards performance on the EEfRT, it is difficult to establish whether reward wanting might be additionally, or alternatively, related to performance. This is particularly challenging to determine without explicit measures of reward wanting and given the complexity of the task. It is also challenging to ascertain whether individuals with MDD may be less willing to expend effort for rewards, specifically because of the effort costs or because of an inability to process reward-related information (e.g. reward magnitude). Additionally, given that perceived failure is characteristic of MDD (Beck, Steer, & Brown, 1996), it is possible that individuals with MDD might make fewer HE/HR selections to minimize the risk of failure. This is since volunteers had to perform a certain number of keypresses within a predetermined amount of time, which is more difficult to achieve on the HE/HR versus LE/LR option. Therefore, individuals with MDD may make fewer HE/HR selections because there is a greater possibility of failure on these trials. Moreover, volunteers are instructed that early HE/HR selections could result in fewer high-value, high-probability trials being presented during the task (Treadway et al., 2009). This information may affect decision-making differently in individuals with MDD, compared to healthy controls. Therefore, due to the complexity of this task, it is difficult to establish which factors may, or may not, have contributed to alterations in reward motivation.

Interestingly, there is also some evidence to suggest that individuals with MDD do not invest less effort to obtain reward, compared to healthy controls (Sherdell et al., 2012). Similar to the EEfRT, volunteers were required to choose between a LE/LR and a HE/HR option. Selecting the LE/LR option meant that volunteers had to click on a moving target fewer times to see a non-humorous cartoon, whereas the HE/HR option required more clicks to view a humorous cartoon. An algorithm calculated the point at which participants were indifferent between selecting either option, indicating the amount of effort they were willing to invest in order to view the preferred cartoons. Unlike the EEfRT, this task did not alter reward magnitude or probability. The authors found that people with MDD did not differ from healthy controls in reward-related effort expenditure. They did, however, find similar to (Yang et al., 2014) that anticipatory anhedonia predicted reward-related effort expenditure. This suggests that MDD volunteers were less willing to invest effort to receive a monetary reward the more anticipatory anhedonia they reported.

Interestingly, another study did not find that individuals with MDD invest less, overall, effort to obtain rewards (Cléry-Melin et al., 2011). In this experiment, volunteers were required to squeeze a handgrip to reach a target, in order to obtain a monetary reward (1cent, 10 cents or 1 euro). They found that, overall, individuals with MDD did not differ in the amount of effort expended to obtain reward, compared to healthy controls. They did find, however, that healthy controls varied how much effort was invested depending on the reward magnitude, whereas individuals with MDD invested a consistent amount of effort across all trials. This may suggest that individuals with HDS do not have impairments in expending effort, but do have difficulties in regulating their behavioural output, depending on reward magnitude (Cléry-Melin et al., 2011).

Similar to consummatory anhedonia, motivational anhedonia in MDD has also been examined using fMRI. Although one neuroimaging study used the EEfRT (Yang et al., 2016), the majority of studies have examined motivational anhedonia using the Monetary Incentive Delay Task (MIDT) (Knutson, Westdorp, Kaiser, & Hommer, 2000). During

the MIDT, a cue signifies the potential to obtain a reward of varying magnitude (anticipatory phase), followed by a target which volunteers have to respond to within a given amount of time (effort phase), in order to obtain a monetary reward (consummatory phase). As indicated in the rodent literature, reward-predicting cues can instigate reward-seeking behaviour (Berridge, Robinson, & Aldridge, 2009) and thus aberrant neural activity to such cues may be related to motivational anhedonia. Similar to findings from the EEfRT (Yang et al., 2016), studies using the MIDT found that people with MDD have reduced activity in the ventral striatum, as well as in the orbitofrontal cortex (OFC), dorsal anterior cingulate cortex (dACC) and hippocampus, to cues predicting potential monetary gain (Knutson et al., 2008; Smoski et al., 2009; Stoy et al., 2012). Interestingly, one study did not observe any neural differences between healthy controls and MDD patients during the anticipatory phase, but did find that activity in the ventral striatum increased with increasing reward magnitude in healthy controls but not MDD patients (Takamura et al., 2017). This may suggest that people with MDD have deficits in processing reward-related information, such as reward magnitude, and translating this into appropriate behavioural output. This is consistent with behavioural evidence, indicating that individuals with HDS do not modulate effort depending on reward magnitude (Cléry-Melin et al., 2011). Moreover, they found that activity in the ventral striatum correlated with reaction time to the target, as well as self-reports of motivation in healthy controls, but not in MDD patients (Takamura et al., 2017). Consequently, neuroimaging studies generally suggest that there is reduced activity during the anticipatory phase in MDD, which may be related to motivational anhedonia.

2.1.3. Summary

Clinically, anhedonia is defined as the loss of interest and pleasure, collapsing impairments in reward motivation and liking into one criterion (American Psychiatric Association, 2013; Argyropoulos & Nutt, 2013; Thomsen et al., 2015). Unfortunately, the term anhedonia is often used to refer to reward deficits more broadly and few studies measure multiple aspects within the same task, and those that do often fail to adequately dissociate them. To address this problem, it has recently been suggested that the term anhedonia should be subdivided, in order to clearly dissociate between different reward-

related constructs (Treadway & Zald, 2011). For instance, motivational anhedonia and consummatory anhedonia have been proposed to refer to reduced motivation to seek rewards and the loss of pleasure, respectively (Treadway & Zald, 2011).

At present, some studies have found evidence to suggest that consummatory anhedonia and motivational anhedonia are apparent in MDD, while others have not found differences between MDD patients and healthy controls in reward liking or motivation. Contradictory findings could be due to a number of factors, including the inability to appropriately measure these different reward dimensions, subtle differences in experimental designs and heterogeneous depressed samples. One of the most fascinating findings in the consummatory literature, is that individuals with MDD do not differ from healthy controls on the amount of pleasure experienced to reward stimuli (Arrondo et al., 2015; Berlin et al., 1998; Clepce et al., 2010; Dichter et al., 2010; Dichter et al., 2004; Forbes et al., 2005; Sherdell et al., 2012; Swiecicki et al., 2009). This is despite individuals with MDD reporting consummatory anhedonia via questionnaires (Berlin et al., 1998; Sherdell et al., 2012; Treadway, Bossaller, et al., 2012; Ubl et al., 2015; Yang et al., 2014). Inconsistent reports of consummatory anhedonia on questionnaires versus in-the-moment ratings have even been found within the same MDD sample, eliminating the possibility that results were inconsistent due to the use of different MDD patients (Sherdell et al., 2012). This raises the intriguing possibility that questionnaires capture a deficit in the ability to accurately anticipate pleasure, as opposed to experience pleasure. Unfortunately, few studies have empirically compared anticipatory with experienced pleasure under controlled laboratory conditions and thus requires further examination.

The literature on motivational anhedonia in MDD relies predominantly on the Effort-Expenditure for Rewards Task (EEfRT), which aims to measure effort-based decision making in the context of monetary reward (Treadway et al., 2009). Evidence from this task suggests that individuals with high depression symptoms (HDS) and a diagnosis of MDD make fewer high-effort/high-reward (HE/HR) selections, compared to healthy controls (Treadway, Bossaller, et al., 2012; Yang et al., 2014). Whilst fewer HE/HR selections may suggest that individuals experiencing high symptoms of depression have motivational anhedonia, it is unclear *why* this is the case. For instance, reduced reward-

related effort expenditure could signify reduced reward wanting, an inability to overcome the costs of effort or impairments in computing cost/benefit analyses (Nunes, Randall, Podurgiel, et al., 2013; Treadway & Zald, 2011). Therefore, further exploration is required, ideally using simpler tasks that measure more than one reward dimension.

Understanding what aspects of reward processing are impaired in individuals experiencing depression, is crucial in order to improve its treatment. This is especially important, since different neurochemicals are thought to underlie different reward aspects, including motivation and liking. This is discussed further in Section 2.2, before the pharmacological treatment of anhedonia is considered in section 2.3.

2.2. The Neurochemical Underpinnings Anhedonia

2.2.1. The Dopaminergic Reward System

Reward processing is generally attributed to two dopaminergic pathways; the mesolimbic and mesocortical pathways (Berridge, 2007; Treadway & Zald, 2011). Broadly speaking, the mesolimbic pathway is associated with reward learning and motivation, whereas the mesocortical system is primarily associated with executive functioning (Treadway & Zald, 2011). The mesolimbic pathway consists of dopamine projections from the ventral tegmental area (VTA), in the midbrain, to the ventral striatum (including the NAcc), amygdala and hippocampus (Treadway & Zald, 2011). Similarly, the mesocortical pathway also originates from the VTA, but projects dopamine neurons to cortical regions such as the OFC, PFC, ACC and insula (Treadway & Zald, 2011). Notably, cortical regions, such as the OFC, vmPFC and insula, also innervate the ventral striatum, which in turn projects back to the cortex via interconnections between the VTA and thalamus (Haber, 2011; Haber & Knutson, 2010). Given the interactions between the two pathways, they are sometimes referred to as the mesocorticolimibic system.

Although the reward system as a whole is often taken to be synonymous with the dopaminergic mesocorticolimbic system, it is crucial to note that reward processing is

multifaceted and incredibly complex (Der-Avakian & Markou, 2012; Treadway & Zald, 2011). As such, it is indisputable that these pathways are unlikely to work in isolation and other regions and neurotransmitters are also likely to be involved. For instance, although less commonly mentioned in direct relation to reward processing, the dopaminergic nigrostriatal pathway and GABA system are also likely to contribute to reward processing (Dichter, Damiano, & Allen, 2012; Dunlop & Nemeroff, 2007; Haber & Knutson, 2010). Further, our understanding of the role of dopamine in reward processing has changed enormously over time. More specifically, accumulating evidence suggests that dopamine is involved in motivational, but not consummatory, processing.

2.2.2. Dopamine and Reward Liking

Hedonic pleasure was originally linked to dopamine, until it became evident that dopamine was not necessary for hedonic processing (Berridge, 2007). One of the most influential studies came from Berridge and colleagues, who examined whether reward wanting and liking are dissociable (Berridge & Robinson, 1998). This was achieved by severely depleting dopamine in areas considered crucial for reward processing, such as the NAcc, and investigating whether rodents with wanting deficits persisted to show intact liking. Wanting deficits were indicated by rats not consuming any freely available cereal food for two weeks. They found that dopamine-depleted rats with impaired wanting displayed hedonic responses (e.g. lateral, and rhythmic, tongue protrusions) to the same extent as control rats. Further, both groups of rats displayed more hedonic reactions to greater reward magnitudes. This suggests that dopamine does not modulate reward liking and is dissociable from reward wanting. Instead, given that dopamine-depleted rodents did not approach and consume any freely available food reward, it was proposed that dopamine may be responsible for ascribing a positive motivational value to a neutral stimulus thereby making it 'wanted' (incentive salience theory) (Berridge & Robinson, 1998). Several studies have since demonstrated that both increasing and decreasing dopamine does not affect the experience of pleasure (Cannon & Palmiter, 2003; Peciña, Cagniard, Berridge, Aldridge, & Zhuang, 2003; Wassum, Ostlund, Balleine, & Maidment, 2011).

Another influential finding that opposes a role of dopamine in reward liking, comes from a study demonstrating that dopamine neurons cease to respond to rewarding outcomes once a cue predicts their delivery. For instance, monkeys were presented with two images with levers underneath each image. The monkeys learnt that pressing one of the levers resulted in a juice reward being delivered, whereas pressing the other lever had no consequence. Initially, dopamine neurons in the VTA and substansia nigra fired to the receipt of the juice, but, throughout learning, this response to the outcome gradually decreased, while dopamine firing to the cue increased (Hollerman & Schultz, 1998). Since, after learning, dopamine neurons no longer responded at the point of reward delivery when pleasure would be experienced, this suggests that dopamine is not a requirement for reward liking. Rather, these phasic dopamine responses to the receipt of an unexpected outcome are thought to operate as a learning signals, known as a prediction error (Hollerman & Schultz, 1998; Schultz, 2007). More specifically, dopamine firing increases to better-than-expected outcomes, is unaffected to expected outcomes, and decreases below baseline to worse-than-expected outcomes. Moreover, dopamine responses to predictive cues track the magnitude and probability of expected outcomes and are thought to guide behaviour (Schultz, 2007). This suggests a role of dopamine in reward-seeking and/or anticipatory pleasure, as opposed to liking.

There is also some evidence in humans to suggest that dopamine does not alter reward liking. For instance, dopamine concentrations in the ventral striatum do not correlate with the subjective experience of pleasure, but does correlate with reward wanting, after the administration of a dopamine-enhancing agent (Evans et al., 2006; Leyton et al., 2002). Further, decreasing dopamine does not alter feelings of euphoria, but does reduce reward wanting (Leyton, Casey, Delaney, Kolivakis, & Benkelfat, 2005). However, it is important to note that there is also some contrasting evidence to suggest that dopamine *is* involved reward liking. For example, one study found that dopamine release in the NAcc correlated with the experience of pleasure during an emotive segment of music (Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011). Furthermore, research has previously found that a dopamine antagonist reduced brain activity in the ventral striatum and ACC, relative to placebo, to the sight and taste of chocolate (McCabe, Huber, Harmer, & Cowen, 2011). Although reward 'wanting' and 'liking' were not dissociated in the latter study, reduced neural activity to pleasurable stimuli may suggest reduced

pleasure. However, given the mounting evidence opposing a direct relationship between dopamine and reward liking, it is possible that these observations are, instead, related to saliency. In line with this, self-reported pleasure, and dopamine in the NAcc, correlated with intensity ratings and physiological responses, including heart rate and respiration (Salimpoor et al., 2011). Therefore, it is possible that dopamine and brain activity in the NAcc during heightened emotional experiences are more related to arousal than pleasure, although these results do not allow a conclusive dissociation between the two. Nevertheless, in light of all the studies reviewed above, the evidence predominately suggests that dopamine is unlikely to be a necessity to experience pleasure.

Hedonic pleasure is, instead, thought to be primarily modulated by the opioid and endogenous cannabinoid systems. More specifically, the opioid and endocannabinoid systems are thought to modulate the experience of pleasure within incredibly localised regions. For instance, microinjections of an endocannabinoid and an μ-opioid agonist to the rostrodorsal quadrant of the NAcc medial shell doubled and nearly quadrupled, respectively, the number of positive hedonic orofacial expressions to sucrose (Castro & Berridge, 2014; Mahler, Smith, & Berridge, 2007; Smith & Berridge, 2007). This suggests that endocannabinoids and opioids in the rostrodorsal quadrant of the NAcc medial shell regulate reward liking. Similarly, microinjections of an μ-opioid agonist into the posterior ventral pallidum also increases the number of positive hedonic orofacial reactions to sucrose solution (Smith & Berridge, 2005, 2007). Further, μ-opioid-induced increases in hedonic pleasure can be prevented using an opioid antagonist in the posterior ventral pallidum and rostrodorsal quadrant of the NAcc medial shell (Smith & Berridge, 2007). This provides further evidence to suggest that opioid activity in these very specific regions modulates reward liking. Intriguingly, microinjections of an μ-opioid agonist to the rostroventral quadrant of the NAcc medial shell did not affect hedonic response (Castro & Berridge, 2014). Additionally, microinjections into the caudal half of the NAcc medial shell elicited negative hedonic responses, suggesting disgust (Castro & Berridge, 2014). This not only suggests that the neural substrate underpinning the experience of pleasure is incredibly localised, but also that the same neurotransmitter can elicit displeasure within close proximity of a region regulating pleasure.

There is also some evidence in humans supporting the involvement of the opioid system in hedonic pleasure. For instance, in healthy volunteers, opioid receptor binding in the PFC/OFC, cingulate cortex, insula and caudate has been found to correlate with subjective reports of euphoria following exercise (Boecker et al., 2008). Further, a line of research demonstrates that opioid antagonism reduces the subjective experience of pleasure and dampens brain activity to reward. For instance, relative to placebo, an opioid antagonist reduces the palatability of, but not appetite for, food (Yeomans & Gray, 1997) and reduces subjective reports of pleasure and zygomatic muscle activity (smiling) to pleasant music (Mallik, Chanda, & Levitin, 2017). On the neural level, there is less activity to a pleasant taste, relative to a neutral taste, under opioid antagonism, in areas such as the lOFC, insula, putamen, posterior cingulate cortex and precentral gyrus (Rabiner et al., 2011). Similarly, research has found that a μ-opioid receptor antagonist reduces dACC activity in healthy volunteers to the sight and taste of chocolate (Murray et al., 2014). Taken together, the evidence suggests that the endogenous opioid system, rather than dopamine, modulates reward 'liking'.

2.2.3. Dopamine and Reward Motivation

Unlike reward liking, there is an abundance of evidence, from the preclinical literature, to suggest that dopamine modulates reward motivation. For instance, numerous studies indicate that rodents invest more effort when dopamine is increased, and invest less effort when dopamine is decreased, especially in the NAcc (Bergamini, Sigrist, et al., 2016; Cagniard, Balsam, Brunner, & Zhuang, 2006; Hamill, Trevitt, Nowend, Carlson, & Salamone, 1999; Soares-Cunha et al., 2016; Trifilieff et al., 2013). For example, by progressively increasing the number of times rodents had to nose-poke into a port in order to obtain a sucrose pellet, it was found that NAcc dopamine-depletion resulted in less expended effort and fewer rewards being attained, compared to vehicle control (Bergamini, Sigrist, et al., 2016). Since locomotion was unaffected by NAcc-dopamine depletions, this suggests that dopamine depletion can reduce motivation to obtain rewards.

Although dopamine has been found to alter reward-related effort expenditure in rodents, as mentioned in section 2.1.2, it is unclear what exactly reward related-effort expenditure represents. The incentive salience theory, suggests that dopamine is responsible for making a stimulus alerting and desired, thus instigating reward-seeking behaviour (Berridge, 2007; Berridge & Robinson, 1998). In keeping with this, studies often interpret increased reward-related effort expenditure as a measure of reward wanting. For instance, one study found that elevating global levels of dopamine, by mutating the dopamine transporter gene, increased reward motivation in an incentive runway procedure (Peciña et al., 2003). Specifically, hyperdopaminergic rodents reached and consumed a food reward more quickly than control rodents. Importantly, this was not because of discrepancies in motor-speed, but because hyperdopaminergic rodents approached the food reward more directly (e.g. fewer pauses and retractions away from the goal box). The authors suggested that dopamine modulates reward wanting, consistent with the incentive salience theory (Peciña et al., 2003).

Although increased reward-related effort expenditure may be related to reward wanting, there are other potential explanations. For instance, dopamine may, more specifically, be related to the overcoming of behavioural costs, as opposed to modulating wanting *per se* (Nunes, Randall, Podurgiel, et al., 2013). Evidence in favour of this notion comes from studies employing the concurrent choice paradigm (CCP). During the CPP, rodents are presented with a lever that can be repeatedly pressed to obtain a food reward and freely available, but less palatable, food (chow). Ordinarily, rodents choose to lever press to obtain the more palatable food source, instead of consuming the freely available chow (Salamone, Arizzi, Sandoval, Cervone, & Aberman, 2002). Similar to the aforementioned studies, experiments using the CCP have found that dopamine depletion and antagonists, particularly when injected into the NAcc, reduces lever pressing to obtain food reward (Koch, Schmid, & Schnitzler, 2000; Nowend, Arizzi, Carlson, & Salamone, 2001; Nunes, Randall, Hart, et al., 2013; Salamone et al., 2002; Sokolowski & Salamone, 1998). However, interestingly, dopamine-impaired rodents consumed *more* of the freely available chow, relative to controls. This suggests that despite working less hard to receive a preferred food reward, rodents still 'wanted' food, thus questioning the role of dopamine in reward wanting (Koch et al., 2000; Nowend et al., 2001; Nunes, Randall, Hart, et al., 2013; Salamone et al., 2002; Sokolowski & Salamone, 1998). Notably,

reduced reward-related effort expenditure and increased consumption of the freely available chow is unlikely to be because of changes in appetite or liking. This is since A) pre-fed rodents make fewer lever presses and consume *less* chow B) dopamine-impaired rodents continue to demonstrate a strong preference for the more palatable food source and C) dopamine-impaired rodents consume comparable amounts of both foods when they are freely available, relative to baseline and saline-treated rodents (Koch et al., 2000; Nunes, Randall, Hart, et al., 2013; Salamone et al., 1991). Moreover, reduced lever-pressing and increased consummation of a freely available alternative is also apparent in dopamine-depleted rodents, when the freely available alternative is the same as the reward for lever pressing (sucrose), but at a lower magnitude (Pardo, López-Cruz, San Miguel, Salamone, & Correa, 2015). This suggests that reduced effort expenditure is not due to satiety or the use of different food sources. Consequently, it is considered that dopamine may be crucial for overcoming behavioural costs in the pursuit of rewards, when other less effortful options are available.

Further evidence in support for dopamine more specifically modulating the overcoming of behavioural costs, comes from studies employing the t-maze procedure. Rodents are presented with the choice between an arm containing 2 freely available pellets (LE/LR) and another arm in which 4 pallets can be obtained after climbing a barrier (HE/HR). Similar to results using the CCP, dopamine depletion and antagonists result in rodents investing less effort for the preferred outcome, i.e. they make more LE/LR and fewer HE/HR arm selections, compared to vehicle controls (Cousins, Atherton, Turner, & Salamone, 1996; Mai, Sommer, & Hauber, 2012; Mott et al., 2009; Pardo et al., 2012). Although the shift in behaviour towards the LE/LR arm could suggest reduced wanting, this is unlikely since dopamine-impaired rodents make just as many HE/HR arm selections as vehicle controls when 1) both arms are blocked and 2) when only the barricaded arm contains pellets (Cousins et al., 1996; Pardo et al., 2012). Moreover, one study found that dopamine-deleted rodents make fewer HE/HR selections despite consuming just as much pellets as vehicle controls, when they are freely available (Mai et al., 2012). This, therefore, suggests that a reduction in HE/HR arm selections in dopamine-depleted rodents is unlikely to be attributable to reduced wanting, decreased liking, or deficits in motor ability to climb the barrier. Rather, it indicates that there may

be impairments in the overcoming of effort costs to obtain reward in the presence of less effortful alternatives.

There is also some evidence in humans to suggest that manipulating dopamine modifies reward motivation. For example, some studies have investigated the relationship between dopamine and subjective reports of reward wanting. This has been examined in individuals either with Parkinson's disease, who have reduced dopamine function and take medication to increase dopamine (levodopa), or in individuals who are addicted to dopamine-enhancing drugs (e.g. amphetamine or cocaine). Results from these studies suggest that increasing dopamine increases self-reported wanting, whereas decreasing dopamine reduces wanting (Evans et al., 2006; Leyton et al., 2005; Volkow et al., 2002). Moreover, self-reported wanting has also been found to correlate with dopamine concentrations in the dorsal and ventral striatum, after administration of dopamine-enhancing agents (Evans et al., 2006; Leyton et al., 2002; Volkow et al., 2002). Consequently, although limited, these studies in humans suggest that enhancing dopamine has beneficial effects on reward wanting.

Dopamine has also been found to influence reward-related effort expenditure in humans. Although limited, findings are consistent with results from the preclinical literature suggesting that increasing dopamine increases reward-related effort expenditure (Chong et al., 2015; Treadway, Buckholtz, et al., 2012; Wardle, Treadway, Mayo, Zald, & de Wit, 2011). For example, enhancing dopamine function in healthy volunteers increased the number of HE/HR selections on the EEfRT, specifically when the probability of being rewarded was low or ambiguous i.e. when the costs were greater (Wardle et al., 2011). Additionally, the percentage of HE/HR selections under low probability trials correlated with dopamine function in the caudate, vmPFC and vlPFC, as measured by positron emission tomography (PET) scanning (Treadway, Buckholtz, et al., 2012). This may suggest that dopamine is involved in reward-related effort expenditure, particularly when the cost of effort is high.

Results from neuroimaging experiments also suggest that dopamine may be involved in reward motivation. For instance, some studies have acutely depleted dopamine in healthy

volunteers and examined brain activity to cues that indicate the potential to obtain a reward (anticipatory phase). Crucially, these cues precede an effort phase, during which a response (e.g. a button press to a target within a restricted time period) is required in order to obtain a reward. These studies have revealed that depleting dopamine reduces brain activity to cues in the cingulate gyrus, NAcc, caudate and amygdala (da Silva Alves et al., 2011; Nagano-Saito et al., 2012). Given that these regions are active during anticipatory phases in the absence of dopamine-depletion and have been related to goal-directed behaviour (Knutson, Fong, Adams, Varner, & Hommer, 2001; Kurniawan, Guitart-Masip, & Dolan, 2011; Salimpoor et al., 2011; Simon et al., 2014), this may suggest that dopamine alters reward motivation. For instance, various preclinical studies have indicated that dopamine in the NAcc is related to reward-related effort expenditure, possibly in the overcoming of behavioural costs (Koch et al., 2000; Nowend et al., 2001; Salamone et al., 1991). Additionally, dopamine in the caudate is related to anticipatory pleasure and neural activity in this regions is greater when reward outcomes are dependent on an active behavioural response (Salimpoor et al., 2011; Tricomi, Delgado, & Fiez, 2004). Further, the ACC, which has connections to the striatum and motor cortex, is implicated in using action-outcome associations to select an appropriate behavioural response to obtain reward (Kurniawan et al., 2011). Taken together, this may suggest a role of dopamine in reward-related motivation. However this could be because of changes in reward wanting and/or alterations in computing cost-benefit analyses.

2.2.4. Is Dopamine Reward-Specific?

As discussed above, there is substantial evidence to suggest a role of dopamine in reward motivation, but not consummation. However, it is important to note that whilst dopamine is frequently discussed as being closely linked to reward processing, there is ample evidence to suggest that dopamine also contributes to aversion processing. For instance, following aversive stimuli (e.g. pinches, social defeat and unpleasant tastes), dopamine increases in regions such as the striatum and PFC in rodents and humans (Anstrom, Miczek, & Budygin, 2009; Bassareo, De Luca, & Di Chiara, 2002; Budygin et al., 2012; Scott, Heitzeg, Koeppe, Stohler, & Zubieta, 2006). Curiously, elevated dopamine

responses to aversive stimuli in regions such as the striatum, mirror those observed in the reward literature, and a number of theories have emerged to account for these results.

Firstly, it is possible that dopamine responds to the rewarding properties of relief *from* aversion, as opposed to aversion *per se* (Navratilova, Atcherley, & Porreca, 2015; Wenzel, Rauscher, Cheer, & Oleson, 2014). For instance, dopamine has been found to increase in the NAcc shell of rats after terminating tail pinches (Budygin et al., 2012; Kalivas & Duffy, 1995). However, within the same study, it was also found that in different regions, such as the NAcc core, dopamine increased to the tail pinch itself (Budygin et al., 2012). This highlights another possibility, that there may be discrete dopamine neurons within distinct subregions that respond to either rewarding or aversive stimuli. Indeed, in favour of this suggestion, studies have identified individual dopamine neurons that activate to rewarding, aversive or alerting stimuli (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Lammel, Ion, Roeper, & Malenka, 2011; Matsumoto & Hikosaka, 2009). Consequently, it has been proposed that dopamine neurons may also respond to stimuli which is motivationally relevant, as opposed to being exclusively activated by reward (Bassareo et al., 2002; Bromberg-Martin et al., 2010; Lammel et al., 2011).

Crucially, if dopamine is involved in both reward and aversion (motivationally salient stimuli) processing, then this could have intriguing implications regarding the potential role of dopamine. Rather than specifically being involved in reward-related motivation, it is possible that dopamine may contribute towards promoting an organism to react actively and adaptively to the environment (Bassareo et al., 2002; Lammel et al., 2011; Matsumoto & Hikosaka, 2009; Wenzel et al., 2014). Therefore, in addition to being involved in reward-seeking behaviour, dopamine may also be involved in actively avoiding aversion (e.g. flight), as opposed to passively responding (i.e. freezing) (Wenzel et al., 2014). In support of this theory, it has been found that dopamine increases in the NAcc core to cues predicting avoidable, but not unavoidable, aversion (Gentry, Lee, & Roesch, 2016; Oleson, Gentry, Chioma, & Cheer, 2012). Furthermore, NAcc dopamine-depleted rodents make fewer escapes, and take longer to escape, from avoidable shock (Bergamini, Sigrist, et al., 2016; Winter et al., 2007). However, the role of dopamine in

aversion processing remains a controversy and is overshadowed by research examining the effect of dopamine on reward processing.

2.2.5. Dopamine in Major Depressive Disorder

As reviewed above, anhedonia (particularly motivational anhedonia) is a reward symptom of MDD that is largely attributed to the dopaminergic system. Consistent with this, a recent review suggests that there is a dopamine deficiency in people with MDD (Belujon & Grace, 2017). For instance, studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) have revealed decreased striatal dopamine transporter (DAT) binding in MDD patients relative to healthy controls (Meyer et al., 2001; Sarchiapone et al., 2006). Reduced striatal DAT binding in MDD is thought to be indicative of DAT downregulation to compensate for reduced dopamine (Meyer et al., 2001; Sarchiapone et al., 2006). This is since DATs reduce the amount of dopamine available at the synaptic cleft and DAT density decreases following dopamine depletion (Belujon & Grace, 2017; Gordon, Weizman, & Rehavi, 1996). In keeping with this, medications which block DATs (thereby preventing the removal of dopamine, thus increasing its availability at the synapse), such as bupropion, improve depression symptoms (Reimherr, Cunningham, Batey, Johnston, & Ascher, 1998; Thase et al., 2005).

A second line of evidence, suggesting that dopamine is reduced in MDD, comes from research demonstrating increased D_2/D_3 receptor binding in the striatum of depressed patients versus controls (Belujon & Grace, 2017; Peciña et al., 2017; Shah, Ogilvie, Goodwin, & Ebmeier, 1997). Increased striatal D_2/D_3 receptor binding in MDD may signify reduced dopamine concentrations (thereby allowing more of the administered radiolabelled ligand to bind with D_2/D_3 receptors), an increase in the amount of D_2/D_3 receptors or an increased affinity of the receptor for the ligand (Dunlop & Nemeroff, 2007). Interestingly, it has been demonstrated that D_2/D_3 receptor binding potential increases following dopamine depletion (Laruelle et al., 1997), suggesting that increased D_2/D_3 receptor binding in MDD may indicate a dopamine deficiency.

Whilst the evidence above suggests that dopamine is reduced in MDD, it is important to note that the evidence is inconsistent. For instance, a review examining DAT availability in MDD indicates that results are incredibly mixed, so much so that it is not possible to conclude whether DAT availability is altered in MDD (Camardese, Di Giuda, et al., 2014). Similarly, there are conflicting results regarding D_2/D_3 receptor binding in MDD, with some studies reporting no group differences (Parsey et al., 2001; Yang et al., 2008). Discrepant results are likely to be the consequence of heterogeneous MDD samples (e.g., length and number of depressive episodes, comorbidity, medication status etc.), the use of different radioligands and methodologies (Camardese, Di Giuda, et al., 2014). Another potential confound is that studies typically recruit patients with a diagnosis of MDD but ignore their presenting symptoms (Camardese, Di Giuda, et al., 2014). Given that the potential for symptom variability in MDD is enormous (Van Loo, De Jonge, Romeijn, Kessler, & Schoevers, 2012), it is possible that there could be different subtypes of MDD (Fletcher et al., 2015). For instance, a melancholic subtype has been identified, with anhedonia being a core symptom (Fletcher et al., 2015). Given the role of dopamine in reward processing, especially motivation (see sections 2.2.1-2.2.3), it is possible that MDD patients experiencing anhedonia, in particular, could have a dopamine deficiency (Fletcher et al., 2015).

Beneficially, there are two studies which specifically recruited depressed volunteers experiencing anhedonia, thereby addressing the potential oversight of an anhedonic subtype of MDD which could have a dopaminergic deficiency (Camardese, De Risio, et al., 2014; Sarchiapone et al., 2006). In support of dopaminergic hypofunction, both studies found that DAT binding was reduced in anhedonic MDD patients compared to healthy controls. However, neither study found correlations between DAT binding and anhedonia ratings. Moreover, one of these studies compared DAT binding between MDD patients with, versus without, anhedonia but did not find any group differences (Camardese, De Risio, et al., 2014). Whilst these results may suggest that reduced DAT binding could be related to depression, rather than specifically an anhedonic subtype of MDD, it is important to note that the sample sizes were incredibly small (10 subjects with, versus 10 subjects without, anhedonia). Furthermore, the anhedonic sample

appeared to have low levels of anhedonia (with an average score of 9 out of a maximum possible score of 56 on the Snaith-Hamilton Pleasure Scale). Therefore, whilst this evidence supports the notion that there is a dopamine deficiency in MDD, more stringent measures are needed to determine whether this could be specifically related to an anhedonic subtype.

Of further interest, one of the studies which specifically examined DAT binding in MDD patients experiencing anhedonia also explored the effects of the dopaminergic enhancing drug, amisulpride (Camardese, De Risio, et al., 2014). Following 3 months treatment with amisulpride, it was found that treatment responders had improved self-reported anhedonia and that DAT binding potential was increased to comparable levels as HCs. This was unlike non-responders who had comparable DAT binding levels as healthy controls both at baseline and post-treatment. This may, therefore, indicate that there could be a subtype of MDD with a dopamine deficiency that can be restored using dopaminergic-enhancing medications. However, although anhedonia improved in treatment responders, both responders and non-responders were considered anhedonic at baseline and thus a dopamine deficiency might not be specific to anhedonia. Nonetheless, it is interesting to consider that this could be, at least in part, the consequence of anhedonia being inadequately measured. Indeed, this study did not measure motivational anhedonia, which is primarily associated with dopaminergic functioning see (sections 2.2.1-2.2.3), and, additionally, self-reports of anhedonia via questionnaires can be problematic (see section 2.1.1). Nevertheless, these results highlight the potential utility of dopaminergic antidepressants for treating some individuals with MDD, which is addressed in the next section.

Taken together, although the evidence is mixed, there is some evidence to suggest that there is a dopamine deficiency in MDD. With improvements in how we recruit MDD samples (e.g., different subtypes, medication status etc.), the utilisation of dopamine-specific ligands and larger sample sizes, a more concise literature might emerge (Camardese, Di Giuda, et al., 2014). Additionally, as reviewed in the next section, there is substantial evidence to suggest that dopaminergic medications can treat MDD, and

more specifically anhedonia, providing further evidence for a dopamine deficiency in MDD.

2.2.6. Summary

Reward processing, as a whole, is largely attributed to the dopaminergic mesocorticolimbic system. However, the traditional view that dopamine modulates reward liking is inconsistent with current evidence indicating that liking is primarily associated with the endocannabinoid and opioid systems. On the other hand, there is ample evidence to suggest that dopamine regulates reward-related effort expenditure, which may indicate that dopamine modulates reward wanting and/or the overcoming of behavioural costs. Taken together, this may suggest that deficits in dopamine function might be related to motivational anhedonia but perhaps not consummatory anhedonia. Notably, although less investigated, there is also some evidence indicating that dopamine is involved in the processing of aversive and alerting stimuli. It is, therefore, possible that dopamine could be related to the processing of motivationally relevant stimuli, promoting active reward seeking *and* aversion avoidance behaviour.

Given that there is evidence to suggest that dopamine alters reward motivation, which is impaired in individuals with MDD, it is possible that dopamine-enhancing agents may be beneficial for treating motivational anhedonia in MDD. This is discussed further in section 2.3.

2.3. The Pharmacological treatment of Anhedonia in Major Depressive Disorder

2.3.1. Selective-Serotonin Reuptake Inhibitors

At present, the first line pharmacological treatment for MDD are selective-serotonin-reuptake-inhibitors (SSRIS) (Grundmann, Kacirova, & Urinovska, 2015; Health, 2017). SSRIs are a class of antidepressants that increase serotonin concentrations by blocking

the serotonin transporter, which ordinarily removes serotonin from the synaptic cleft back into the presynaptic neuron (Stahl, 1998).

Although SSRIs are effective at improving depression symptoms, relative to placebo (Arroll et al., 2005; Gibbons, Hur, Brown, Davis, & Mann, 2012; Gorman, Korotzer, & Su, 2002; Olie, Gunn, & Katz, 1997), research suggests that they might be more effective at treating some symptoms than others. More specifically, it has been suggested that SSRIs might be effective at improving symptoms such as low mood and anxiety, but not anhedonia (Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Nutt et al., 2007; Shelton & Tomarken, 2001). This suggestion stems from evidence demonstrating that anhedonia takes longer to subside than anxiety, predicts longer time to achieve remission, and is a common residual symptom following SSRI treatment (Boyer, Tassin, Falissart, & Troy, 2000; McMakin et al., 2012; Nierenberg et al., 1999).

In addition to potentially ineffectively treating anhedonia, there is also evidence to suggest that SSRIs may even *induce* anhedonia (McClintock et al., 2011; Opbroek et al., 2002; Price, Cole, & Goodwin, 2009). For instance, in a sample of 428 MDD patients treated with the SSRI, citalopram, 40% of patients reported developing a loss of interest (McClintock et al., 2011). Further, SSRI-treated patients commonly complain of emotional blunting, with both positive and negative affect being dampened, potentially related to a general loss of interest (Opbroek et al., 2002; Price et al., 2009). Consistent with this, we have previously found that citalopram reduces brain activity during both reward and aversion processing in healthy volunteers, which may underlie blunted affect (McCabe, Mishor, Cowen, & Harmer, 2010).

One reason why SSRIs might not be the most effective treatments for anhedonia is that they do not directly enhance dopamine, which, as detailed in section 2.2, is the neurotransmitter that plays a crucial role in reward processing (Blier & Briley, 2011; Dunlop & Nemeroff, 2007). In fact, there is even some evidence to suggest that some SSRIs *inhibit* dopaminergic pathways via serotonin $_{2C}$ receptors (5-HT$_{2C}$R), which may explain why they are ineffective treating anhedonia (Blier & Briley, 2011; Di Matteo, De

Blasi, Di Giulio, & Esposito, 2001; Dremencov, El Mansari, & Blier, 2009; Prisco & Esposito, 1995). As a result, it has been proposed that medications that increase catecholamines, such as dopamine and noradrenaline, may be more effective at improving anhedonia in MDD (Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Nutt et al., 2007; Shelton & Tomarken, 2001). Two catecholamine-enhancing antidepressants that may have beneficial effects on anhedonia are bupropion and agomelatine.

2.3.2. Bupropion

Similar to how SSRIs increase serotonin availability, bupropion increases dopamine and noradrenaline levels in the synaptic cleft by preventing their reuptake (Dwoskin, Rauhut, King-Pospisil, & Bardo, 2006; Stahl et al., 2004). Bupropion is also an antagonist at nicotinic acetylcholine receptors (nAChR), which is thought to aid smoking cessation (Dwoskin et al., 2006; Stahl et al., 2004). Demonstrating antidepressant properties, bupropion is superior to placebo at improving depression symptoms, with one study demonstrating efficacy after as early as three weeks (Reimherr et al., 1998; Thase et al., 2005). Moreover, there is evidence to suggest that bupropion is comparable to SSRIs and serotonin and noradrenaline reuptake inhibitors (SNRIs) at improving depression symptoms (Croft et al., 1999; Maneeton, Maneeton, Eurviriyanukul, & Srisurapanont, 2013; Thase et al., 2005). Additionally, there have been some observations to suggest that bupropion may be useful for treating SSRI-resistant depression (Fava et al., 2003; Rosso, Rigardetto, Bogetto, & Maina, 2012). This may suggest that whilst different classes of antidepressants might, overall, be equally effective at achieving remission, they may do so by improving different symptoms. Consistent with this, it has been reported that bupropion is more effective than SSRIs at improving hypersomnia and fatigue (Cooper, Tucker, & Papakostas, 2014; Papakostas et al., 2006). Moreover, unlike SSRIs, bupropion is not associated with adverse effects including weight-gain or sexual dysfunction, and is generally better tolerated (Abler et al., 2011; Moreira, 2011; Thase et al., 2005). Consequently, the literature suggests that bupropion is an effective antidepressant and may target different symptoms than SSRIs.

Given the hypothesis that dopaminergic antidepressants might be particularly effective for treating anhedonia in MDD (Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Nutt et al., 2007; Shelton & Tomarken, 2001), it is reasonable to predict that bupropion might be effective at improving anhedonia in MDD. Consistent with this, bupropion has been found to improve the energy, pleasure and interest items on the Inventory of Depressive Symptomatology-Self Report, relative to placebo (Jefferson et al., 2006). Another study reported that, compared to placebo, bupropion improved anhedonia (Tomarken, Dichter, Freid, Addington, & Shelton, 2004). However, when reviewing the anhedonia-related items within the questionnaire used, it could be argued that a more accurate interpretation of these findings might be that bupropion improved positive affect and/or energy rather than anhedonia. Bupropion has also been reported to alleviate apathy in three case studies, which may suggest a particular improvement in the "loss of interest" dimension of anhedonia (Corcoran, Wong, & O'Keane, 2004). Interestingly, one study used fMRI to examine the effects of 7-day treatment with bupropion (150 mg/d) or with the SSRI paroxetine (20mg/d) on brain activity to erotic videos in healthy males. Relative to placebo, bupropion increased brain activity in the amygdala, thalamus and frontal cortex, whereas paroxetine decreased brain activity in the ventral striatum, midbrain and ACC (Abler et al., 2011). Furthermore, direct comparison between the two drugs revealed that bupropion increased brain activity in the ventral striatum, midbrain, ACC and frontal cortex more so than paroxetine (Abler et al., 2011). Increased neural activity to pleasurable stimuli following bupropion treatment may suggest that bupropion has reward potentiating effects. Given that paroxetine, on the other hand, decreased neural activity, these results may also support the notion that dopaminergic antidepressants might be more effective at treating anhedonia than SSRIs.

There is also evidence from the preclinical literature to suggest that bupropion might have beneficial effects on reward processing. More specifically, whilst there are no known studies that have examined bupropion in relation to reward consummation, there is some evidence demonstrating that bupropion enhances reward-related motivation. For instance, bupropion increases lever pressing for food reward and decreases the consumption of freely available chow, suggesting increased reward-related effort expenditure even when an alternative food source is available at less cost (Bruijnzeel & Markou, 2003; Randall et al., 2015). Furthermore, bupropion increases lever pressing to

activate a rewarding visual stimulus, an effect not prevented by a nAChR antagonist (Palmatier et al., 2009). This not only suggests that bupropion enhances reward-related effort expenditure for rewards other than food, but also that these effects are not caused by bupropion's antagonistic effects at nAChRs (Palmatier et al., 2009). Moreover, bupropion has been reported to reverse the debilitating effects of dopamine-depletion on reward-related effort expenditure. For instance, dopamine-depletion reduces lever pressing and barrier climbing to obtain food reward and increases consumption of freely available chow, an effect that can be reversed by bupropion treatment (Nunes, Randall, Hart, et al., 2013; Randall et al., 2015). Interestingly, bupropion-induced increases in lever-pressing and decreased chow intake in dopamine-depleted rats is prevented by pre-treating rodents with dopamine antagonists and a selective inhibitor of dopamine transporters (Yohn et al., 2015). Moreover, whereas bupropion improves motivational deficits induced by dopamine-depletion, the SSRI fluoxetine exacerbates these motivational deficits (Yohn et al., 2015). Therefore, this may offer some support for the notion that dopaminergic antidepressants might be more beneficial than serotonergic antidepressants for treating reward-related deficits, specifically motivational anhedonia.

2.3.3. Agomelatine

Another pharmacological agent that may improve symptoms of anhedonia is agomelatine. Agomelatine uniquely increases dopamine and noradrenaline in the PFC by disinhibiting 5-HT_2R, which are receptors that ordinarily inhibit the release of dopamine and noradrenaline upon stimulation (Stahl, 2007). Agomelatine is also an agonist at melatonin (MT1 and MT2) receptors, which is the mechanism through which it is thought to improve sleep disturbances by restoring circadian rhythms (De Bodinat et al., 2010; Sansone & Sansone, 2011). Additionally, agomelatine has also been reported to be an antagonist at 5-HT_{2B} receptors. The clinical relevance of 5-HT_{2B} receptors is unknown, however, they are sparse in the brain and they appear to not influence monoaminergic transmission (Alex & Pehek, 2007; Millan et al., 2003).

The efficacy of agomelatine (25-50mg/day) at improving symptoms of depression has been demonstrated using various double-blind, randomised, placebo-controlled trials (Kennedy & Emsley, 2006; Loo, Hale, & D'haenen, 2002; Stahl et al., 2010) and in a recent meta-analysis which integrated both published and unpublished data (Taylor, Sparshatt, Varma, & Olofinjana, 2014). Meta-analyses have suggested that agomelatine may be more effective than SSRIs and SNRIs at improving depressive symptoms after 6-12weeks, while the effect of these antidepressants are comparable at 24 weeks (Huang et al., 2014; Kasper et al., 2013). Therefore, evidence suggests that agomelatine can alleviate depression symptoms and may have a more rapid-onset than conventional antidepressants.

Although limited, there is some evidence to suggest that agomelatine is effective at improving anhedonia in individuals with MDD. For instance, two 8-week open label trials found that agomelatine significantly reduced scores on a questionnaire measuring consummatory anhedonia in MDD patients, relative to baseline (Di Giannantonio et al., 2010; Martinotti et al., 2012). Impressively, agomelatine significantly improved self-reports of anhedonia after as little as 1 week and was superior to the SNRI, venlafaxine, after 1 and 8 weeks of treatment (Di Giannantonio et al., 2010; Martinotti et al., 2012). Moreover, there is some evidence to suggest that agomelatine improves motivation, as indicated through self-report in over 1,500 MDD patients (Gorwood et al., 2015). This may suggest that agomelatine might be beneficial for motivational anhedonia. Furthermore, one double-blind, randomised trial found that, compared to an SSRI, agomelatine was less associated with emotional blunting (Corruble, de Bodinat, Belaïdi, & Goodwin, 2013). For instance, only 28% of patients treated with agomelatine reported that their emotions lacked intensity, compared to 60% of patients treated with an SSRI. Whilst emotional blunting may not directly measure anhedonia, it is plausible that blunted positive and negative affect could be related to "the loss of interest" domain of anhedonia. Further, in healthy volunteers, agomelatine increased the recognition of positive, relative to negative, self-referential words (Harmer et al., 2011). Whilst increased memory of positive affective stimuli is not a direct measure of anhedonia, it may suggest increased processing of positive stimuli which could possibly extend to reward processing. Taken together, although the majority of evidence is either preliminary or indirect, it is plausible that agomelatine may have beneficial effects on reward processing.

Findings from the few studies that have examined the effects of agomelatine on reward processing in rodents, suggest that agomelatine may potentiate reward processing. For instance, agomelatine has been found to increase sucrose preference and consumption in rodent models of depression, possibly suggesting beneficial effects on consummatory anhedonia (El Yacoubi, Dubois, Gabriel, Mocaër, & Vaugeois, 2011; Papp, Gruca, Boyer, & Mocaër, 2003). Further, in relation to motivational anhedonia, 6-day agomelatine treatment increased reward-related effort expenditure on a progressive ratio schedule task; however, this effect represented a trend and was not statistically significant (Bergamini, Cathomas, et al., 2016).

Although the majority of studies in humans are based on open-label, pilot data, and evidence from the preclinical literature is sparse, results are in favour of agomelatine having beneficial effects on motivational and consummatory anhedonia. Additionally, it is conceivable that agomelatine could have reward-potentiating effects given its action at 5-HT_{2C}R, which are known to modulate reward-motivated behaviour (Hayes & Greenshaw, 2011; Thome & Foley, 2015). For instance, 5-HT_{2C}R agonists negatively impact reward motivation in rodents, including reducing the number of lever presses and the breaking point on a progressive reinforcement ratio schedule, which can be prevented by pre-administrating a 5-HT_{2C}R antagonist (Bezzina et al., 2015; Cunningham et al., 2011; Higgins et al., 2013). In addition to preventing the debilitating effects of 5-HT_{2C}R agonists on reward-motivated behaviour, 5-HT_{2C}R antagonists can augment reward-related effort expenditure (Bailey et al., 2016; Simpson et al., 2011). For instance, rodents treated with a 5-HT_{2C}R antagonist perform more lever presses to obtain food rewards and consume less freely available chow, suggesting an increase in reward motivation (Bailey et al., 2016; Simpson et al., 2011). Crucially, the above effects of 5-HT_{2C}R on reward-motivated behaviour are unlikely to be the result of changes in general locomotor movement, appetite, or non-reward-specific arousal. This is since 1) performance is only enhanced on active, and not inactive, levers, 2) performance is also potentiated when rodents have to hold down (as opposed to press) a lever and c) the time taken to collect rewards and the number of rewards consumed is unaffected (Bailey et al., 2016; Cunningham et al., 2011; Higgins et al., 2013; Simpson et al., 2011).

The facilitating effects of 5-HT_{2C}R antagonists on reward-related effort expenditure is likely to be the result of its catecholamine enhancing properties. Studies using microdyalisis have revealed that 5-HT_{2C}R agonists decrease dopamine release in the NAcc, striatum and frontal cortex, whilst having no effect on serotonin (Di Matteo, Di Giovanni, Di Mascio, & Esposito, 2000; Gobert et al., 2000). Consistent with this, electrophysiological results have indicated that 5-HT_{2C}R agonists reduce the firing rate of dopaminergic and noradrenergic neurons in the VTA and LC, respectively (Di Matteo et al., 2000; Gobert et al., 2000). Crucially, pre-treatment with a 5-HT_{2C}R antagonist prevents dopamine reduction in the NAcc and VTA dopaminergic neuronal firing, whereas 5-$HT_{2A/B}$ receptors appear to have no influence on dopamine, noradrenaline or serotonin (Di Matteo et al., 2000; Gobert et al., 2000). This suggests that 5-HT_{2C}R inhibit dopamine release in the mesocorticolimbic system, an effect that can be counteracted via 5-HT_{2C}R antagonists. Intriguingly, it is plausible that the activation of 5-HT_{2C}R, and the resulting inhibition of the dopaminergic mesocorticolimbic pathway, could potentially underlie the inability of SSRIs to treat anhedonia (Blier & Briley, 2011). Therefore, agomelatine is a particularly interesting antidepressant to examine in relation to reward processing, as it prevents activity at 5-HT_{2C}R.

2.3.4. Summary

At present, antidepressants which increase the amount of serotonin available at the synaptic cleft, SSRIs, are the recommended first-line treatment for MDD (Grundmann et al., 2015). Although SSRIs are effective at improving depression symptoms, relative to placebo, they are criticised for ineffectively treating anhedonia (Argyropoulos & Nutt, 2013; Arroll et al., 2005; Dunlop & Nemeroff, 2007; Gibbons et al., 2012; Gorman et al., 2002; Nierenberg et al., 1999; Nutt et al., 2007; Olie et al., 1997; Shelton & Tomarken, 2001). This may, potentially, be because SSRIs do not directly target, and some may even reduce, dopamine (Blier & Briley, 2011; Di Matteo et al., 2001; Dremencov et al., 2009; Dunlop & Nemeroff, 2007; Prisco & Esposito, 1995). Consequently, it has been proposed that antidepressants which increase catecholamines might be more effective at improving anhedonia in MDD (Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Nutt et al., 2007; Shelton & Tomarken, 2001). Bupropion and agomelatine are two antidepressants,

which increase dopamine and noradrenaline via reuptake inhibition and 5-HT_{2C}R disinhibition, respectively (Dwoskin et al., 2006; Stahl, 2007; Stahl et al., 2004). Although there is limited empirical investigation of the effects of bupropion and agomelatine on anhedonia, particularly in humans, it is reasonable to predict based on their pharmaceutical profiles and the available literature, that they could enhance reward processing. However, how bupropion and agomelatine affects reward anticipation, effort and consummation in the human brain remains to be examined.

2.4. Principle questions

This thesis contributes to the literature examining anhedonia in relation to MDD and its treatment. As reviewed above, despite evidence indicating that motivation and liking are dissociable aspects of reward processing (e.g. (Berridge & Robinson, 1998), few experimental tasks measure both aspects or, adequately, dissociate between them. Consequently, it is unclear what aspects of reward processing are impaired in individuals experiencing depression symptoms. For instance, there are mixed results as to whether or not there are impairments in reward motivation (motivational anhedonia) and reward liking (consummatory anhedonia) in individuals with high depression symptoms and MDD (see review in section 2.1). With regards to the treatment of anhedonia in MDD, evidence suggests that the current first-line pharmacological treatments (SSRIs) are ineffective at improving anhedonia (Boyer et al., 2000; McMakin et al., 2012; Nierenberg et al., 1999). This may be because SSRIs do not directly enhance, and may even reduce, dopamine, which is the neurotransmitter largely attributed to reward processing (Blier & Briley, 2011; Di Matteo et al., 2001; Dremencov et al., 2009; Dunlop & Nemeroff, 2007; Prisco & Esposito, 1995). As a result, it has been suggested that antidepressants which increase catecholamines might be more effective at improving anhedonia in MDD (Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Nutt et al., 2007; Shelton & Tomarken, 2001). Whilst there is a strong rationale behind this notion, this is primarily based on preclinical research and, thus, further research in humans is required.

Three papers are included in this thesis, which aim to expand on the literature examining anhedonia in MDD and its treatment, in order to help address some unanswered

questions. Although the focus of this thesis is on reward processing, given that dopamine has also been implicated in aversion processing, we also examined aversion processing. This was to assist with the interpretation of our results, allowing us to ascertain whether our results were specific to reward processing.

2.4.1. What Aspects of Reward Processing are Impaired in Individuals with High Symptoms of Depression?

As reviewed in section 2.1, given that it is unclear what specific aspects of reward processing are impaired in individuals experiencing depression symptoms, paper 1 aimed to investigate this in individuals with high depression symptoms (HDS). More specifically, I developed a simple effort-based task that aims to measure reward, and aversion, -related effort expenditure, by progressively increasing the amount of effort required to obtain the taste of chocolate and avoid an unpleasant taste, respectively. Manipulating effort using a progressive-ratio schedule, is similar to how motivation is examined in rodents, beneficially, allowing cross-comparisons to be made with the preclinical literature (Thomsen, 2015). Furthermore, the simple nature of this task, allowed us to specifically examine the effect of increasing the cost of effort on reward and aversion motivation. The amount of effort invested to obtain reward was compared between individuals who scored high, versus low, on the Beck Depression Inventory (Beck et al., 1996). To measure multiple aspects of reward and aversion processing, and to assist with the interpretations of our results, wanting, anticipated pleasure, liking and intensity were also examined through self-report. It was hypothesised that, compared to individuals with low depression symptoms (LDS), individuals with HDS would invest less effort to obtain reward and would report reduced reward wanting, anticipated pleasantness and intensity. Consistent with emerging research reviewed in section 2.1, we predicted that individuals with HDS would report greater consummatory anhedonia via a questionnaire, but would not differ in how pleasant they considered the chocolate taste.

2.4.2. How do Antidepressants that Increase Catecholamines Affect Reward Processing in the Healthy Human Brain?

Although it has been suggested that antidepressants which increase dopamine and noradrenaline might be effective at improving anhedonia in MDD (Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Nutt et al., 2007; Shelton & Tomarken, 2001), this notion has received little empirical investigation in humans. Bupropion and agomelatine are two antidepressants which increase dopamine and noradrenaline via different mechanisms. However, how bupropion and agomelatine affect brain activity during reward processing in the human brain remains to be examined. Consequently, papers 2 and 3 investigated how bupropion and agomelatine, respectively, affect reward and aversion processing in the human brain. Since evidence suggests that brain activity is altered in individuals experiencing HDS (Epstein et al., 2006; Knutson et al., 2008; Pizzagalli et al., 2009; Smoski et al., 2009; Stoy et al., 2012; Yang et al., 2016), we examined the neural effects of these two antidepressants in healthy volunteers. This allowed us to characterise the effects of these antidepressants on the human brain, without confounds such as heterogeneous symptoms, previous treatment, and symptom severity. Given that these are, to the best of our knowledge, the first studies to examine these antidepressants in the human brain in relation to reward and aversion anticipation, effort and consummation, this was an appropriate first step before examination in MDD samples. Both studies utilised double-blind, placebo-controlled, cross-over designs, in which healthy volunteers took an antidepressant and placebo for 7 days, separated by a two-week washout phase. Volunteers underwent an fMRI scan after 7 days of drug, and 7 days of placebo, treatment. During the fMRI scan, volunteers saw an image which indicated the opportunity to work to obtain the taste of chocolate (anticipatory phase) before button pressing (effort phase) to try to obtain the pleasant taste (consummatory phase). Based on the notion that dopaminergic antidepressants might be useful for anhedonia, we predicted that both antidepressants would increase brain activity during reward processing.

2.5. References

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3. Paper 1: Impaired Anticipatory Pleasure in Individuals with High Symptoms of Depression during a Progressive Ratio Effort task.

Manuscript in preparation.

Title:

Impaired Anticipatory Pleasure in Individuals with High Symptoms of Depression during a Progressive Ratio Effort task.

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Abstract

Background

Although the loss of interest or pleasure (anhedonia) is a core symptom of depression, it is unclear how various aspects, such as anticipation, motivation and consummation, contribute to depression. Therefore, we examined these components through subjective report and reward-related effort expenditure, using a novel task of motivation in participants with high, versus low, depression symptoms (HDS and LDS, respectively).

Methods

One hundred and fifty participants were recruited. Fifty-four participants had HDS (scoring ≥ 17 on the Beck Depression Inventory II, BDI) and ninety-six participants had no current or previous psychiatric diagnosis (healthy controls). A subset of fifty-three healthy controls had LDS (scoring ≤7 on the BDI). We developed a progressive ratio task using button presses, to either obtain a pleasant taste or avoid an unpleasant taste. Subjective ratings of wanting, expected pleasantness, pleasantness and intensity were also collected.

Results

Compared to LDS participants, HDS participants reported increased consummatory anhedonia via a questionnaire. However, groups did not differ on any subjective ratings during the task. HDS participants underestimated how pleasant the pleasant taste would be. Although there were no group differences on the PR task, compared to LDS participants, a subset of HDS participants underestimated their performance.

Conclusions

Our study demonstrates that people with HDS underestimate how much pleasure will be experienced to pleasant stimuli, and a subset of HDS volunteers underestimate their performance. This study extends the knowledge base on anhedonia and indicates that components, such as anticipatory pleasure, could be targets for interventions.

Introduction

Defined as the loss of interest or pleasure, anhedonia is a core symptom of Major Depressive Disorder (MDD) that predicts depression severity and remission (American Psychiatric Association, 2013; McMakin et al., 2012; Vrieze et al., 2014). However, anhedonia can be subdivided into anticipatory, motivational and consummatory components (Berridge & Robinson, 2003). Anticipatory anhedonia is conceptualised as the reduced ability to *anticipate* pleasure, whilst motivational anhedonia refers to reduced *effort* to obtain reward and consummatory anhedonia is the inability to *experience* pleasure. Currently, these components are not well understood in MDD, as most studies do not adequately dissociate between them (Argyropoulos & Nutt, 2013; McCabe, 2018; Rizvi, Pizzagalli, Sproule, & Kennedy, 2016).

Dissociating how different dimensions of reward processing contribute to MDD is likely to improve the treatment of, clinically defined, anhedonia (Thomsen, Whybrow, & Kringelbach, 2015). Pharmacologically, this is especially the case given that different aspects of reward processing are thought to be underpinned by different neurochemical pathways. For instance, dopamine is no longer thought to modulate the experience of pleasure and is instead associated with the endogenous opioid and cannabinoid systems (Berridge & Robinson, 1998; Der-Avakian & Markou, 2012; Smith & Berridge, 2007). Reward prediction and motivation on the other hand, is strongly attributed to the dopaminergic system, particularly the mesolimbic and mesocortical pathways (Berridge & Robinson, 1998; Der-Avakian & Markou, 2012). It may also assist with the development of psychotherapies, for example by identifying potential treatment strategies. It is, therefore, plausible that with an improved understanding of how different aspects of reward processing are affected in MDD, treatments could be refined to target specific symptoms (Argyropoulos & Nutt, 2013; Thomsen et al., 2015).

Despite being a core symptom of MDD, a recent review reports that there is more behavioural evidence opposing a hedonic deficit in MDD than there is in favour (Thomsen et al., 2015). Although people with MDD consistently report a consummatory

deficit via questionnaires (Sherdell, Waugh, & Gotlib, 2012; Treadway, Bossaller, Shelton, & Zald, 2012; Yang et al., 2014), an overwhelming number of empirical studies find that they report liking various pleasant stimuli comparably to healthy controls (HC) (Arrondo et al., 2015; Clepce, Gossler, Reich, Kornhuber, & Thuerauf, 2010; Dichter, Smoski, Kampov-Polevoy, Gallop, & Garbutt, 2010; Dichter, Tomarken, Shelton, & Sutton, 2004; Forbes, Miller, Cohn, Fox, & Kovacs, 2005; Sherdell et al., 2012; Swiecicki et al., 2009). Discrepant results between questionnaires and in-the-moment ratings of reward stimuli may suggest that people with MDD have impairments in accurately predicting or recalling pleasure, rather than experiencing pleasure per se. Consistent with this, people with MDD and high depression symptoms (HDS) report, via questionnaires, anticipating less pleasure to rewarding events than HC (Sherdell et al., 2012; Yang et al., 2016; Yang et al., 2014). However, there are few studies that have experimentally compared in-the-moment ratings of anticipated pleasure with experienced pleasure to a given reward (Chentsova-Dutton & Hanley, 2010; Wu et al., 2017). One naturalistic study, which collected ratings of anticipated and experienced pleasure to daily activities, found that individuals with MDD anticipate experiencing less pleasure, compared to healthy controls (Wu et al., 2017). However, this study also found that people with MDD experience less pleasure compared to HC, suggesting that their prediction of reduced pleasure was accurate (Wu et al., 2017). Nevertheless, given the lack of empirical evidence, further exploration is warranted using designs whereby the reward is identical for both the clinical and comparison groups and when anticipated and experienced pleasure is measured within close proximity of reward delivery.

Although there are numerous tasks designed to examine reward motivation in rodent models of depression, there are limited human paradigms. All but two studies examining physical effort expenditure to obtain reward in MDD use the Effort-Expenditure for Rewards Task (EEfRT). The EEfRT examines motivational anhedonia via decision making between investing low effort to obtain a lower monetary reward (LE/LR) or high effort to receive a higher monetary reward (HE/HR) (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). Supporting the notion that people with MDD have impaired reward motivation, people with MDD and HDS make fewer HE/HR selections compared to HC (Treadway et al., 2012; Yang et al., 2014). However, given

the complexity of the task, it is difficult to establish what factors may, or may not, have contributed to alterations in reward motivation. For instance, it is unclear if fewer HE/HR selections suggests reduced reward wanting, an inability to overcome the costs of effort, or an inability to compute cost-benefit analyses (Salamone, Arizzi, Sandoval, Cervone, & Aberman, 2002; Treadway et al., 2012; Treadway & Zald, 2011). Furthermore, it is intriguing that reduced reward-related effort expenditure in MDD has not been found in studies that did not use the EEfRT (Cléry-Melin et al., 2011; Sherdell et al., 2012). However, one study did find that individuals with MDD do not modulate effort depending on reward magnitude (Cléry-Melin et al., 2011). Consequently, further examination of reward motivation in MDD is required, ideally using simpler tasks to help decipher the reasoning behind reduced motivation.

As a result, we designed a simple task that examines effort expenditure, via key-pressing, to obtain a primary reward (taste of chocolate). Similar to preclinical models, effort was directly manipulated via increasing the number of keypresses required to obtain the reward, using a progressive ratio (PR) schedule. On each trial, volunteers could either invest effort to receive a reward (HE/HR) or could terminate the trial after investing no, or some, effort to obtain a less desirable outcome (neutral taste) (LE/LR). Using an "opt-out" versus an "opt-in" method allowed us to examine intended and executed effort. For instance, terminating a trial without making any keypresses may suggest that there was no intention to obtain the reward (and, thus, may not be "wanted"), whereas performing some keypresses before ceasing to invest effort, may suggest that the reward was desired but the effort required to obtain it was not worthwhile. We also examined other aspects of reward processing to facilitate the interpretation of task performance by collecting ratings of the tastes (wanting, expected pleasantness, pleasantness and intensity). Based on the previous literature, we predicted that people with HDS would invest less effort to obtain reward than individuals with low depression symptoms (LDS). Unlike previous tasks, we also examined motivation to avoid aversion (unpleasant taste) to help determine whether performance was affected differently depending on the valence of the outcome. Given the unsettled debate as to whether people with MDD are hypersensitive or hyposensitive to aversion (Rottenberg, Gross, & Gotlib, 2005), we hypothesized that that

there would be a significant difference in effort expenditure to avoid aversion between participants with HDS and LDS.

Method

Participants

Data from 97 HC, classified as having no current or previous psychiatric diagnosis, was collected (data combined from 2 studies to increase power) and volunteers were recruited via the online research management system SONA. A subset of HC (n=54) were specifically recruited for the purposes of this study, and were classified as individuals with LDS if they scored ≤7 on the Beck Depression Inventory-II (BDI) (Beck, Steer, & Brown, 1996). Individuals who scored ≥17 on the BDI were included in the HDS group (n=55) and were recruited from SONA and flyers/posters. Data from 1 volunteer with LDS and 1 volunteer with HDS was removed from analyses, due to a lack of task compliance. Using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007), a total sample size of 76 was identified to obtain 80% power at α=0.05, based on an effect size (f=0.165) taken from a previous paper examining reward motivation in depression (Sherdell et al., 2012). However, given task differences and that our data was likely to have more variability, a larger sample of 100 participants in the between-groups analysis was desired.

Exclusion criteria for all volunteers included being aged outside 18-40 years, a history of seizures or epilepsy (due to a flashing image during the task), lactose intolerance and injury to the dominant hand (e.g. breakage or sprain). An additional exclusion criterion only for HC was current/previous psychiatric condition, as assessed with the DSM-IV Structured Clinical Interview (SCID) (Spitzer, Williams, Gibbon, & First, 2004).

The study was located in the Department of Psychology at the University of Reading and participants were either reimbursed via course credit or £20 for completing the study. Ethical approval was obtained from the University of Reading Research Ethics Committee and all subjects provided written consent prior to participation. All volunteers were also given a debrief form after completing the study, which signposted mental health resources if needed.

Questionnaires and Materials

Volunteers completed the BDI (Beck et al., 1996) and were screened using the SCID (Spitzer et al., 2004). Following the screening session, volunteers also completed trait measures including the State-Trait-Anxiety Inventory-Y2 (STAI) (Spielberger, 1983) and the Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford, & Barratt, 1995). Since the reward in our study was the taste of chocolate, volunteers also completed a questionnaire measuring chocolate liking and consumption (Rolls & McCabe, 2007). Given that the time between trial initiation and reward increased over trials (as trials progressively required more effort, thus more time to complete), volunteers also completed the monetary choice questionnaire (MCQ) (Kirby, Petry, & Bickel, 1999). This was to allow examination of whether task performance was affected by any group differences in delay discounting. To ascertain mood state, volunteers completed a mood visual analogue scales (VAS) prior to starting the task. After completing the task, volunteers rated how hard they felt they worked (0 not very much - 10 very much) on a VAS. Similar to our previous studies, volunteers completed a range of trait questionnaires online after the session, including the Temporal Experience of Pleasure scale (TEPS) (Gard, Kring, Gard, Horan, & Green, 2007) and Behavioural Inhibition/Activation Scales (BIS/BAS) (Carver & White, 1994). Given that we use taste stimuli, we also administered the Eating Attitudes Test (EAT) (Garner, Olmsted, Bohr, & Garfinkel, 1982).

Stimuli

An image of chocolate, mouldy chocolate and a glass of water was used, in addition to a pleasant (Belgian chocolate drink), unpleasant (chocolate drink mixed with apple and ginger juice) and a neutral taste (25 x 10^{-} mol/L KCL and 2.5x10^{-} mol/L $NaHCO_3$ in distilled H_2O). Solutions were delivered through three teflon tubes held together by a plastic mouthpiece and connected by a one-way syringe-activated check valve (Model 14044-5, World Precision Instruments, Inc.). This allowed 2mL of solution to be manually delivered by the experimenter, when prompted via a dual-way monitor. The tubes were passed through a partition separating the experimenter and participant.

General Procedure

Volunteers recruited specifically for the purposes of this study, completed the BDI (Beck et al., 1996) and were included if they scored ≤7 (LDS) or ≥17 (HDS). All volunteers were asked to not consume any chocolate 24hr prior to their session and to consume a light breakfast/lunch. This was to ensure that volunteers were not full before testing and to allow the chocolate stimulus to be rewarding. All participants were screened using the SCID (Spitzer et al., 2004) to exclude for current/previous psychiatric disorder in the HC group and to gain demographic details of the HDS group. Eligible volunteers had their height and weight measured to calculate Body Mass Index (BMI) and completed trait questionnaires, followed by state mood questionnaires. The experimenter prepared the tastes whilst volunteers completed questionnaires. Following questionnaire completion, a measure of how quickly volunteers could press a button on a keyboard within 15s across 3 trials (response speed) was taken, to compare groups for motor ability. This was completed again after completing the experimental task so that effects of fatigue could be examined. Participants then tried each of the tastes (pleasant, unpleasant and neutral) before having the task explained to them and completed four practice trials (2 reward, 2 aversion). After finalising any questions, participants completed the experimental task. During task completion, the experimenter and volunteer were separated by a partition to minimise distraction and social desirability. After completing the task, volunteers completed a VAS measuring how hard they felt they worked. Volunteers were debriefed and sent trait questionnaires to complete outside of the session.

Experimental Task

The task (approx. 20min) was designed to measure how much effort volunteers were willing to invest (via keypressing) in order to obtain a pleasant taste and to avoid an unpleasant taste. The task utilised a block-design, consisting of a reward block and aversion block (counterbalanced, 12 trials per block). Block type was cued at the start of each trial by a visual stimulus (chocolate or a mouldy chocolate picture). On each trial, volunteers could invest effort either to obtain the taste of chocolate (reward block) or to avoid an unpleasant taste (aversion block), by pressing ‘z’ or ‘n’ (pseudorandomized to maintain attention) repeatedly with the index finger of the dominant hand. Pressing the

button gradually filled a bar and volunteers had to fill the bar within an unrestricted amount of time (to eradicate the possibility of failing due to speed), in order to receive a more desirable taste (chocolate on reward trials and neutral taste on aversion trials). If volunteers did not want to work to obtain the pleasant taste, or to avoid the unpleasant taste, they could press 'q' to end the trial (quit) but received a less desirable taste (neutral taste on reward trials and aversive taste on aversion trials). Quitting terminated the trial and not the task (i.e. every volunteer was presented with the full 12 trials on each block). To avoid participants quitting to speed up the task, they were told that pressing 'q' would not make the testing session end any faster. Unbeknown to participants, those who pressed 'q' were kept behind after the task for the approximated time it would have taken to complete the task without pressing 'q' (determined from piloting). To remind volunteers of the potential outcomes, an image of either water, chocolate or mouldy chocolate was at either end of the progress bar. As trials ascended, the amount of effort required to obtain the more desirable taste increased under a PR-5 schedule, starting from 27 keypresses (i.e. 27, 32, 42, 57…1754). Filling the bar or pressing 'q' prompted written feedback of which taste was earnt, before a screen informed that the taste (2ml) would be delivered to their mouth. On each trial, volunteers rated 'wanting', 'expected pleasantness' (before investing effort), 'pleasantness' and 'intensity' (after investing effort) of the tastes on a VAS (0 not very much - 100 very much). Each trial ended with a screen reading 'rest' and volunteers were told that this would vary in duration and should relax their hand. Unbeknown to participants, the rest duration varied depending on their performance (see S1 in the Supplementary Material). See Figure 1 for a visual depiction of a reward trial.

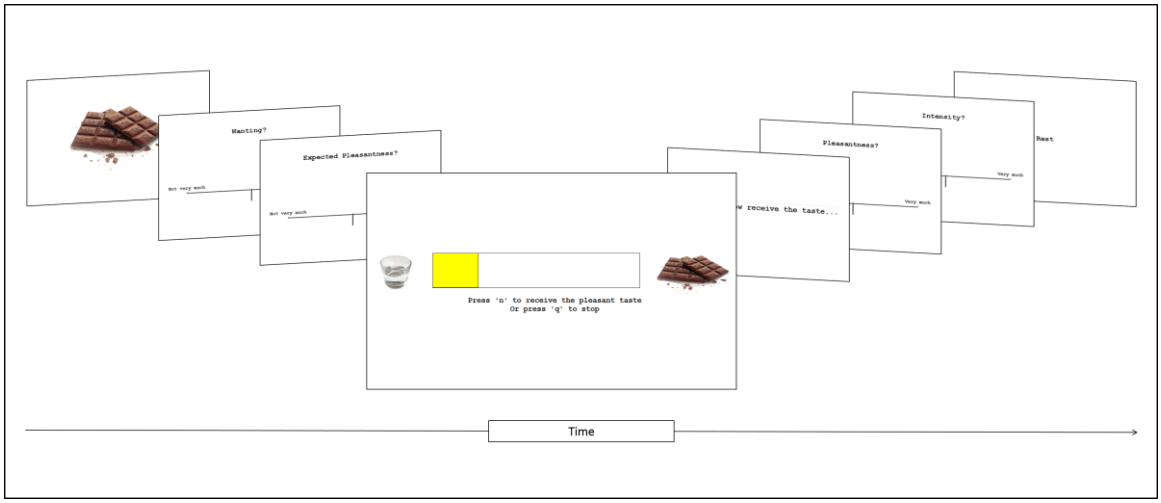

Figure 1. Visual depiction of a reward trial.

Data Analysis

Data analyses were first performed within volunteers with HC (n=96 combined from two studies to increase power) and HDS (n=54), separately. Comparisons were then conducted between volunteers with LDS (n=53) and HSD.

The experimental task and pre/post response speed measure were generated using E-prime. The dependent variables for the experimental task were the total number of keypresses made to obtain the pleasant taste and to avoid the unpleasant taste (maximum possible 1754 per block), the average number of keypresses made per second (kp/s), the number of quits and the earliest break point (trial number of the first quit; maximum possible 12 per block and non-quitters were attributed 12), on each block.

Data were analysed using SPSS and where assumptions were violated, non-parametric tests were utilized. Categorical data was analysed using Chi-squares (between group analyses) and McNemar tests (within group analyses). All other within and between groups comparisons were analysed using t-tests. For completeness, we also examined the relationship between effort expenditure (keypresses) with questionnaire responses and subjective ratings of the tastes, which can be found in S2. Data is reported uncorrected for multiple comparisons, unless results changed after correcting for the number of

statistical tests performed within each group for each section (corrected values are reported in brackets). See S3 for further details on data analysis.

Results

Demographic details

Full demographic details are presented in Table 1 and further details specifically related to volunteers with HDS can be found in S4. Volunteers with LDS and HDS were matched on gender, handedness and chocolate liking. Compared to LDS volunteers, HDS volunteers were significantly older and craved more chocolate. Further, HDS volunteers scored higher on the BDI, STAI, EAT, BIS-11 and BIS. They also had greater anhedonia scores on the TEPS anticipation, TEPS consummation and BAS fun seeking subscales. HDS volunteers also had a higher BMI, consumed chocolate more frequently, scored higher on the MCI (i.e. prefer immediate rewards) and scored lower on the BAS drive and reward responsiveness subscale, but these five effects did not survive correction for multiple comparisons. Where groups significantly differed on questionnaires that did not measure mood or anhedonia, correlations were performed with task performance to determine whether they affected reward/aversion related motivation (S5).

Table 1. Demographic details

	HC	**LDS**	**HDS**	***Test Statistic***	**Sig[a]**
Age (years)	19.00 (1.00)	19.00 (1.00)	20.00 (4.00)	*U*=690.500	<0.001
Gender (F/M)	82/96 (85.42%)	47/53 (88.68%)	43/54 (79.63%)	$\chi^2(1)=1.639$	0.200
BDI	2.00 (5.75)	1.00 (5.00)	24.50 (10.25)	*U*=0.00	<0.001
BMI	21.30 (3.14)	21.36 (3.07)	23.41 (5.89)	*U*=1026.500	0.017 (0.288 [b])
Handedness (right)	86/96 (89.58%)	49/53 (92.45%)	49/54 (90.74%)	$\chi^2(1)=0.102$	0.750
TEPS Anticipation	48.00 (7.00)	49.00 (6.75)	44.00 (10.50)	*U*=828.00	<0.001
TEPS Consummation	39.50 (9.00)	41.00 (9.00)	36.00 (7.50)	*U*=884.500	0.001
EAT	3.00 (4.00)	3.00 (4.00)	8.00 (12.00)	*U*=607.00	<0.001
Chocolate Craving	6.00 (2.00)	6.00 (2.00)	7.50 (1.25)	*U*=823.500	<0.001
Chocolate Liking	8.00 (1.00)	8.00 (1.00)	9.00 (2.00)	*U*=1225.00	0.186
Chocolate frequency	2.00 (2.00)	2.50 (2.50)	4.00 (3.50)	*U*=992.00	0.009 (0.147 [b])

STAI	34.00 (8.00)	33.00 (7.00)	53.00 (9.75)	U=109.500	<0.001
BAS Drive	11.00 (2.00)	11.00 (2.00)	10.00 (2.00)	U=1002.00	0.015 (0.247 [b])
BAS Fun seeking	12.50 (2.75)	13.00 (2.50)	11.00 (3.00)	U=9.00	0.002
BAS Reward Responsiveness	17.00 (3.00)	17.00 (3.00)	16.00 (4.00)	U=987.500	0.011 (0.194 [b])
BIS	21.00 (5.00)	21.00 (4.25)	24.00 (5.00)	U=557.00	<0.001
BIS-11	58.50 (11.75)	59.00 (10.50)	67.13 (14.00)	U=665.500	<0.001
MCQ	0.006 (0.01)	0.006 (0.01)	0.0158 (0.02)	U=933.00	0.006 (0.110 [b])

HC, healthy controls; LDS, low depression symptoms; HDS, high depression symptoms; BDI, Beck Depression Inventory; BMI, Body Mass Index; TEPS, Temporal Experience of Pleasure Scale; EAT, Eating Attitudes Test; STAI, State Trait Anxiety Inventory; BAS, Behavioral Activation Scale; BIS, Behavioral Inhibition Scale; BIS-11, Barratt Impulsiveness Scale; MCQ, Monetary Choice Questionnaire.

Data are median (interquartile range), except gender and handedness which are frequencies (percentages).

[a]Comparisons between volunteers with LDS and HDS

[b]Did not survive correction for multiple comparisons

Pre-task mood

Pre-task mood data are presented in S6. Compared to volunteers with LDS, volunteers with HDS were more anxious, sad, agitated and hungry before the task. Further, they were less motivated and less happy. Given that hunger was unlikely to be related to depression, a correlation was performed to determine whether hunger was related to task performance, which was not significant (S6).

Response Speed

HC

Volunteers made fewer kp/s before versus after the task, suggesting that the task did not induce fatigue (Z=-4.060, p<0.001, r=-0.42).

HDS

Similar to HC, volunteers with HDS made fewer kp/s before, versus after, the task (Z=-2.441, p=0.015, r=-0.34).

LDS vs HDS

There were no significant group differences in pre-task response speed (U=1276.500, p=0.515, r=-0.06), suggesting that groups were matched on motor ability. There were also no significant differences in the change of kp/s pre/post task (U=1326.00, p=0.866, r=-0.02), suggesting that response speed for both groups was similarly affected by the task (S7).

Subjective Ratings

See S8 for aversion intensity results.

HC

Although volunteers liked the pleasant taste and disliked the unpleasant taste to a similar degree (Z=-0.207, p=0.836, *r*=-0.02), they wanted to avoid the unpleasant taste more than they wanted to obtain the pleasant taste (*Z*=-7.536, p<0.001, *r*=-0.78) and expected to dislike the unpleasant taste more than they expected to like the pleasant taste (*Z*=-6.975, p<0.001, *r*=-0.72). Whereas there were no differences between expected and experienced pleasantness of the pleasant taste (*Z*=-0.661, p=.508, *r*=-0.07), volunteers expected to dislike the unpleasant taste more than they actually disliked it (*Z*=-6.906, p<0.001, *r*=-0.73).

HDS

Similar to HC, those with HDS wanted to avoid the unpleasant taste more than they wanted to obtain the pleasant taste (*Z*=-5.333, *p*<0.001, *r*=-0.74), expected to dislike the unpleasant taste more than they expected to like the pleasant taste (*Z*=-5.062, *p*<0.001, *r*=-0.70) and expected to dislike the unpleasant taste more than they actually disliked it (*Z*=-3.562, *p*<0.001, *r*=-0.49). However, unlike HC, those with HDS disliked the unpleasant taste *more* than they liked the pleasant taste (Z=-2.081, *p*=0.037 (*p*=0.187 corrected), *r*=-0.29) and liked the pleasant taste *more* than they expected to like it (Z=-2.412, p=0.016 (*p*=0.079 corrected), *r*=-0.33), but these two effects did not survive correction for multiple comparisons.

LDS vs HDS

Although there was a trend towards volunteers with HDS rating the unpleasant taste *more* unpleasant (*Z*=-1.875, *p*=0.061, *r*=-0.18), we found no significant group differences on any of the ratings (Figure 2); wanting (reward: *Z*=-1.371, *p*=0.170, *r*=-0.13; aversion: *Z*=-0.723, *p*=0.470, *r*=-0.07); expected pleasantness (reward: *Z*=-0.079, *p*=0.937, *r*=-0.01; aversion: *Z*=-0.574, *p*=0.566, *r*=-0.06); pleasantness (*Z*=-1.182, *p*=0.237, *r*=-0.11); reward intensity (*Z*=-1.403, *p*=0.161, *r*=-0.14).

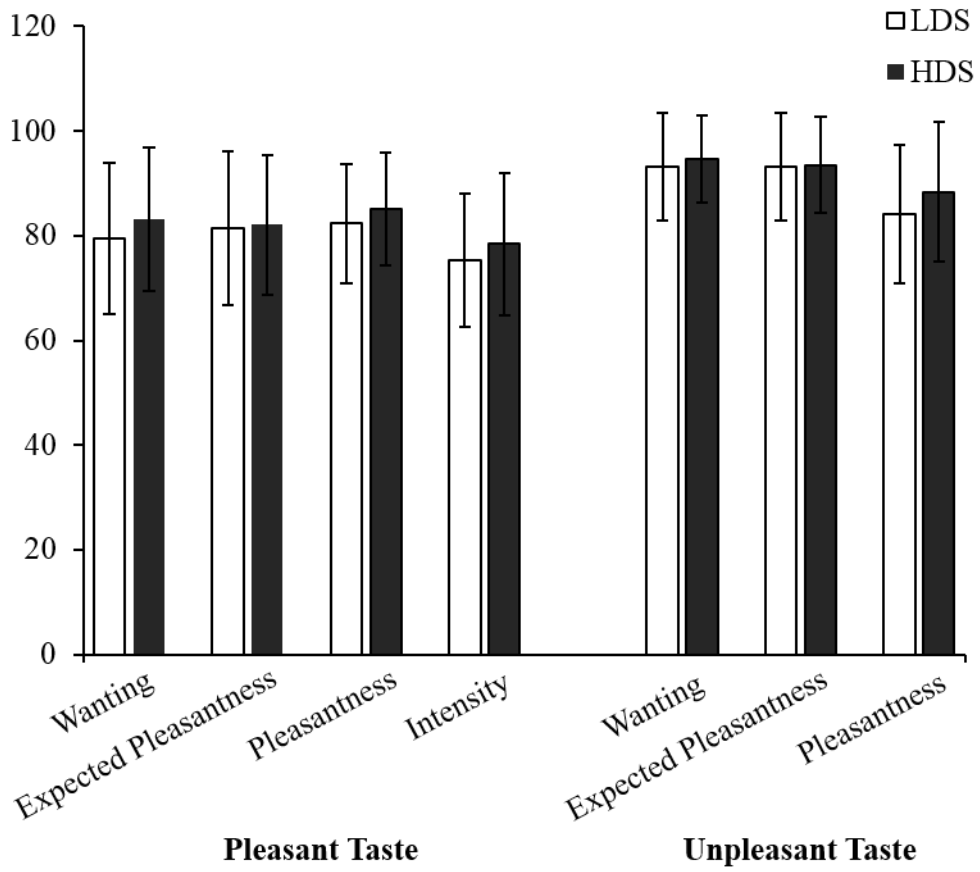

Figure 2. Subjective ratings of the pleasant and unpleasant taste for volunteers with low depression symptoms and high depression symptoms. Bar plots represent the means and error bars show the standard deviations.

Effort and speed to obtain reward and avoid aversion

HC

Consistent with volunteers wanting to avoid the unpleasant taste more than they wanted to obtain the pleasant taste, volunteers made significantly more keypresses to avoid the unpleasant taste than to obtain the pleasant taste (Z=-5.178, p<0.001, r=-0.54). This suggests that HC were more motivated to avoid the unpleasant taste. There was no significant difference in the number of kp/s made to obtain reward or avoid aversion (Z=-1.332, p=0.183, r=-0.14).

HDS

Similar to HCs, volunteers with HDS made significantly more keypresses to avoid the unpleasant taste than to obtain the pleasant taste (Z=-3.774, p<0.001, r=-0.53). There was no significant difference in the number of kp/s made to obtain reward or avoid aversion (Z=1.337, p=0.18, r=-0.19).

LDS vs HDS

There were no significant group differences in the number of keypresses or kp/s made to obtain the pleasant taste, suggesting that volunteers with LDS and HDS invested similar amounts of effort, and worked just as fast, to obtain reward and avoid aversion (Figure 3) (reward keypresses: U=1340.00, p=0.797, r=-0.03; reward kp/s: U=1220.00, p=0.311, r=-0.10; aversion keypresses: U=1304.00, p=.692, r=-0.04; aversion kp/s: U=1294.00, p=0.708, r=-0.04).

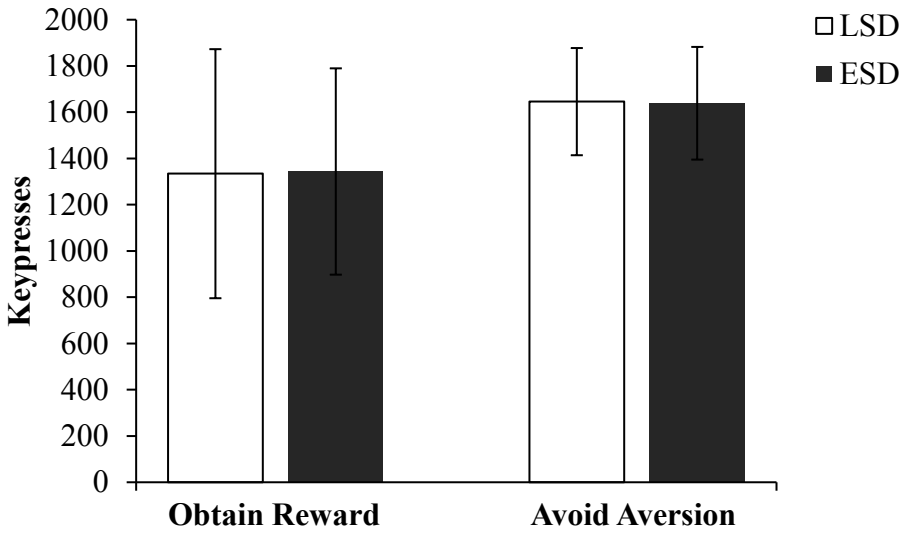

Figure 3. The number of keypresses made to obtain reward and avoid aversion by volunteers with low depression symptoms and high depression symptoms. Bar plots represent the means and error bars show the standard deviations.

Quitting behaviour

S9 summarises the descriptive statistics for quitting behaviour.

HC

Volunteers were more likely to quit (p=0.001), made significantly more quits *(*Z=-5.000, p<0.001, r=-0.52) and quit earlier (Z=-3.477, p=0.001, r=-0.36) on the reward, versus aversion, block. On average, volunteers made 24 keypresses (IQR=51) and 29 keypresses (IQR=50) before quitting on the reward and aversion block, respectively. This was significantly greater than zero keypresses (reward: Z=780.00, p<0.001, r=-0.76; aversion: Z=190.00, p<0.001, r=-0.75), indicating that, on average, volunteers invested some effort before quitting, as opposed to ending the trial without investing any effort.

HDS

Similar to HCs, HDS volunteers made significantly more quits (Z=-3.507, p<0.001, r=-0.50) and quit earlier (Z=-2.917, p=0.004, r=-0.41) on the reward versus aversion block. Although HDS volunteers were more likely to quit on the reward block, this did not survive correction for multiple comparisons (p=0.013 (p=0.064 corrected)). On average, volunteers made 23 keypresses (IQR=75) and 45 keypresses (IQR=75) before quitting on the reward and aversion block, respectively. This was significantly greater than zero (reward: Z=325.00, p<0.001, r=-0.81; aversion: Z=105.00, p=0.001, r=-0.82).

LDS vs HDS

Neither volunteers with LDS or HDS were more likely to quit on either block (reward: $\chi^2(1)$=0.474, p=0.491; aversion: $\chi^2(1)$=0.315, p=0.575). Moreover, there were no group differences on the number of quits, earliest breakpoint or number of keypresses made before quitting, on either block (reward quits: U=1299.00, p=0.591, r=-0.05; aversion quits: U=1303.00, p=0.685, r=-0.04; reward breakpoint: U=1294.00, p=0.562, r=-0.06; aversion breakpoint: U=1293.00, p=.580, r=-0.05; reward keypresses before quitting: U=299.00, p=0.272 , r=-0.15; aversion keypresses before quitting: U=98.00, p=0.812, r=-0.05).

Wanting Ratings on Quitted Trials

HC

On average, volunteers wanted the pleasant taste (Mdn=66.00, IQR=20.57) and did not want the unpleasant taste (Mdn=92.25, IQR=18.19) above the level of indifference (50/100 representing neither wanting or not wanting) on trials where they quit (reward: Z=1102.00, p<0.001, r=0.63; aversion: Z=329.50, p<0.001, r=0.77). This suggests that HC wanted the pleasant taste and did not want the unpleasant taste on trials where they quit.

HDS

Similar to HCs, HDS volunteers wanted the pleasant taste (Mdn=59.00, IQR=22.07) and did not want the unpleasant taste (DS: Mdn=86.83, IQR=26.25) above the level of indifference on trials where they quit (reward: Z=360.500, p=0.002, r=0.57; aversion: Z=135.00, p=0.001, r=0.87).

LDS vs HDS

Groups did not differ in how much they wanted the pleasant taste, or on how much they did not want the unpleasant taste, on trials where they quit (reward: U=376.00, p=0.990, r<0.001; aversion: U=83.500, p=0.235, r=-0.22).

Perceived versus expended effort

HC

Overall effort expenditure correlated with how hard volunteers felt they worked, suggesting that they had a good representation of their performance (r_s=0.295, p=0.005).

HDS

Unlike HC, overall effort expenditure did not correlate with how hard HDS volunteers felt they worked, suggesting that they were inaccurate at retrospectively evaluating their performance (r_s=0.169, p=0.240).

LDS vs HDS

Groups did not differ in how hard they felt they worked (U=1203.500, p=0.336, r=-0.09). Figure 4 depicts the relationship between perceived and expended effort in the volunteers with LDS and HDS. Visually, it appeared that HDS volunteers were more likely, than LDS volunteers, to underestimate how hard they worked when they invested high amounts of effort. To examine this further, a median split was performed on perceived effort within the LDS and HDS groups, to separate volunteers into those who had high or low perceived effort ratings. Then the difference in the percentage of expended effort and perceived effort was computed, to determine whether volunteers overestimated or underestimated how much effort was invested. The difference between expended and perceived effort was then compared between LDS and HSD volunteers with low perceived effort. This confirmed that HDS volunteers who reported low perceived effort underestimated how much effort they invested, significantly more so than LDS volunteers (U=230.50, p=.02).

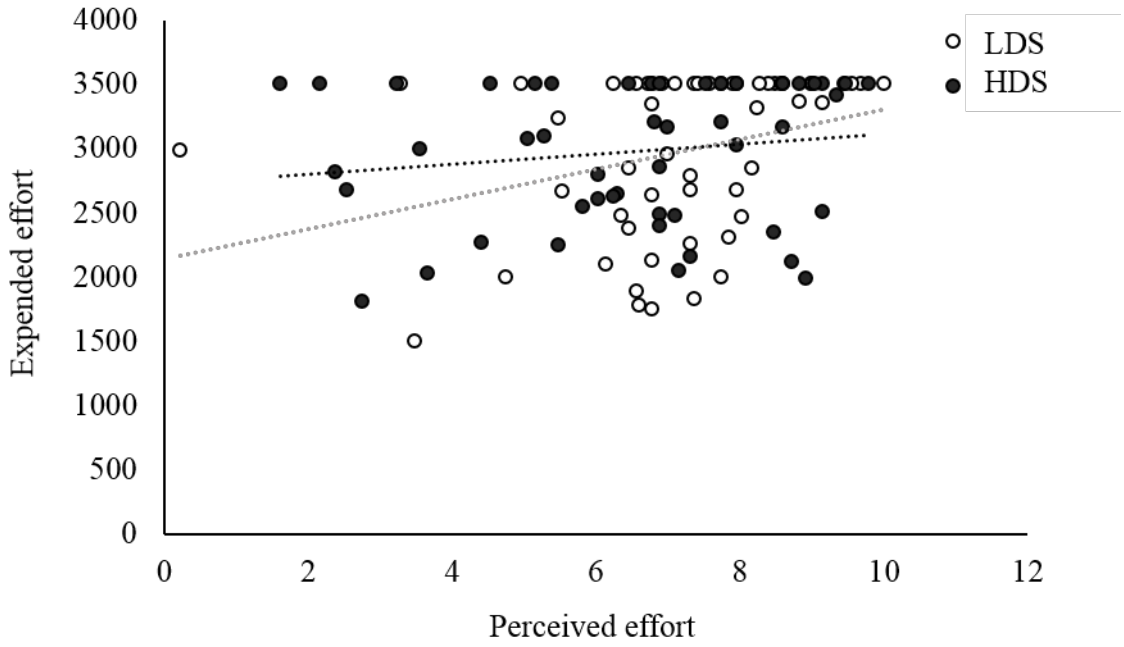

Figure 4. Correlation between the total number of keypresses made and how hard volunteers with low, and high, depression symptoms felt they worked.

Discussion

This study aimed to examine different aspects of reward and aversion processing in people with HDS versus LDS. Reward and aversion motivation was measured via the number of keypresses invested to obtain a pleasant taste and to avoid an unpleasant taste, respectively, using a novel PR task. Reward and aversion wanting, expected pleasantness, pleasantness and intensity were also investigated through self-report. Similar to previous studies (Cléry-Melin et al., 2011; Sherdell et al., 2012), we found no evidence to suggest that individuals with HDS invested less effort to obtain a reward. Further, we found no group differences in effort expenditure to avoid aversion or subjective ratings of the tastes. Interestingly, we did find evidence to suggest that individuals with HDS underestimated expected pleasure and a subset of HDS volunteers underestimated how much effort they actually invested. This is interesting, in that our results may suggest that altering negative biases, in relation to anticipatory pleasure and performance, may be useful therapeutic targets in MDD.

Consistent with previous studies (Sherdell et al., 2012; Treadway et al., 2012; Yang et al., 2014), we found that individuals with HDS report feeling less pleasure than individuals with LDS, via the TEPS questionnaire. However, volunteers with LDS and HDS did not differ in their pleasantness ratings of the chocolate taste. Our results support the abundance of studies that find that individuals with HDS do not have deficits in experiencing pleasure after reward delivery (Arrondo et al., 2015; Clepce et al., 2010; Dichter et al., 2010; Dichter et al., 2004; Forbes et al., 2005; Sherdell et al., 2012; Swiecicki et al., 2009). Inconsistent self-reports of consummatory anhedonia via questionnaires, but not immediately after receiving a reward, may suggest that questionnaires capture impairments in accurately anticipating pleasure, as opposed to experiencing pleasure. In line with this suggestion, we found that volunteers with HDS underestimated how pleasant the chocolate taste would be (although this was a trend effect after correcting for multiple comparisons). This may have crucial clinical implications, as it may be beneficial to encourage patients to record and evaluate anticipated pleasure with experienced pleasure during psychotherapy. This is since recognizing a tendency to underestimate pleasure may encourage patients to engage in,

and not withdraw from, positive activities, which is the aim of Behavioral Activation (Hopko, Lejuez, Ruggiero, & Eifert, 2003).

Similar to previous research (Cléry-Melin et al., 2011; Sherdell et al., 2012), we did not find that individuals with HDS invested less effort to obtain reward compared to volunteers with LDS. However, studies using the EEfRT do find that individuals with HDS make fewer HE/HR selections, compared to HCs (Treadway et al., 2012; Yang et al., 2014). It is possible that we, and others (Sherdell et al., 2012), did not find reduced reward-related effort expenditure because our tasks did not require effort to be performed within a time-limit. This is unlike the EEfRT, which requires volunteers to perform a certain number of keypresses within a predetermined amount of time. Since it is more challenging to complete HE/HR versus LE/LR trials, it is possible that depressed volunteers make fewer HE/HR selections on the EEfRT out of fear of failure. This is especially possible given that negative biases are characteristic of MDD and perceived failure is even measured on the BDI (Beck et al., 1996).

Another potential explanation is that people with HDS might have impairments in computing cost/benefit analyses (Treadway et al., 2012; Treadway & Zald, 2011). For instance, individuals with HDS may either 1) overestimate the costs (other than effort) and/or underestimate the benefits of rewards, or 2) have impairments in integrating vast amounts of information into a cost/benefit analysis (Treadway et al., 2012; Treadway & Zald, 2011). Our task was very simple and only manipulated the amount of effort required to obtain a fixed reward. The EEfRT, on the other hand, alters the difficulty, reward magnitude and probability of being rewarded after successfully completing a trial. Volunteers are required to process all of this information and decide between the LE/LR and HE/HR option within 5 seconds. It is, therefore, possible that individuals with HDS might not have impairments in overcoming the costs of effort to obtain rewards, as our results suggest, but could have deficits in integrating a multitude of reward-related information to make effort-based decisions (Treadway et al., 2012; Treadway & Zald, 2011). Future research should examine this further and include measures of working

memory, to help identify whether impairments are reward-specific or related to more general impairments in higher-level cognitive functions (Snyder, 2013).

Although we found that volunteers with LDS and HDS volunteers did not differ in the amount of effort invested to obtain reward and avoid aversion, we did find that perceived effort only correlated with expended effort in HC, and not volunteers with HDS. More specifically, there was a subset of HDS volunteers with low perceived effort who underestimated how hard they worked, compared to LDS volunteers. This might suggest that there is a subgroup of volunteers with depression symptoms who underestimate their performance, perhaps consistent with negative cognitive biases (Hindash & Amir, 2012). It is conceivable, that if a subgroup of volunteers with HDS underestimate their performance then they may experience less positive feedback from expending effort (e.g. feel less achievement). Speculatively, overtime this could cause withdrawal from positive events, which could make them less enjoyable in the future. As a result, future studies should examine whether underestimating performance (and anticipatory pleasure) could predispose motivational anhedonia and consummatory anhedonia in MDD.

Although effort expenditure is a commonly used in the preclinical literature to measure 'wanting', it has been demonstrated that an organism may desire an outcome yet not invest effort to obtain it (Salamone et al., 2002). Intriguingly, we found that on trials where volunteers quit, they still wanted to obtain reward and avoid aversion. Further, on average, volunteers predominantly terminated a trial after keypressing, as opposed to investing zero effort, suggesting that they intended to work but did not execute this. Taken together, this may suggest that volunteers ceased to invest effort, not because of reduced 'wanting' per se, but because they could not overcome the cost of effort (Salamone et al., 2002). This has fundamental implications regarding the interpretation of studies using effort expenditure as a measure of 'wanting', since this may more precisely measure the ability to overcome the costs of effort (Salamone et al., 2002).

Regardless of depression symptoms, we found that volunteers were more motivated to avoid aversion than to obtain reward. For instance, volunteers reported wanting to avoid aversion more than they wanted to obtain reward. Consistent with this, volunteers invested more effort, made fewer, and later, quits when avoiding aversion relative to obtaining reward. Additionally, volunteers expected to dislike the unpleasant taste more than they actually disliked it, potentially representing a negative bias that could drive motivation to expend effort. Notably, although volunteers with LDS and HDS disliked the unpleasant taste to a similar degree, greater disliking ratings in the HDS, versus LDS, group did approach significance prior to correcting for multiple comparisons. This should, therefore, be examined further, as it may suggest that individuals with HDS are hypersensitive to aversion. Moreover, whilst volunteers with LDS and HDS invested comparable amounts of effort to avoid aversion, we did encounter a ceiling effect in our aversion data. Consequently, we cannot eradicate the possibility that groups could have differed on the aversion block if the task had been more difficult.

In summary, our results suggest that individuals with HDS do not have impairments in expending effort to obtain reward or avoid aversion using a novel PR task. We also found that volunteers with LDS and HDS did not differ on subjective reports of wanting, expected pleasantness, pleasantness and intensity of a pleasant, and an unpleasant, taste. We did find, however, that a subset of HDS volunteers underestimated how much effort they invested. Our results may suggest that impairments in accurately anticipating pleasure and evaluating expended effort may predispose motivational anhedonia and consummatory anhedonia. Future research should explore this further, as there may be therapeutic benefits in helping patients recognise these biases.

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Conflict of interest

The authors have no conflict of interest.

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4. Paper 2: Enhanced Neural Response to Anticipation, Effort and Consummation of Reward and Aversion during Bupropion Treatment.

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Title:

Enhanced Neural Response to Anticipation, Effort and Consummation of Reward and Aversion during Bupropion Treatment.

Running Title:

Effect of Bupropion on Neural Reward.

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Abstract

Background

We have previously shown that the selective serotonergic re-uptake inhibitor, citalopram, reduces the neural response to reward and aversion in healthy volunteers. We suggest that this inhibitory effect might underlie the emotional blunting reported by patients on these medications. Bupropion is a dopaminergic and noradrenergic re-uptake inhibitor and has been suggested to have more therapeutic effects on reward-related deficits. However, how bupropion affects the neural responses to reward and aversion is unclear.

Methods

17 healthy volunteers (9 female, 8 male) received 7 days of bupropion (150 mg/day) and 7 days of placebo treatment, in a double-blind crossover design. Our functional Magnetic Resonance Imaging task consisted of 3 phases; an anticipatory phase (pleasant or unpleasant cue), an effort phase (button presses to achieve a pleasant taste or to avoid an unpleasant taste) and a consummatory phase (pleasant or unpleasant tastes). Volunteers also rated wanting, pleasantness and intensity of the tastes.

Results

Relative to placebo, bupropion increased activity during the anticipation phase in the ventral medial prefrontal cortex (vmPFC) and caudate. During the effort phase, bupropion increased activity in the vmPFC, striatum, dorsal anterior cingulate cortex and primary motor cortex. Bupropion also increased medial orbitofrontal cortex, amygdala and ventral striatum activity during the consummatory phase.

Conclusions

Our results are the first to show that bupropion can increase neural responses during the anticipation, effort and consummation of rewarding and aversive stimuli. This supports the notion that bupropion might be beneficial for depressed patients with reward-related deficits and blunted affect.

Introduction

Defined as the inability to experience pleasure from normally rewarding stimuli, anhedonia is one of the two main diagnostic criteria for depression. Studies examining the effects of the current antidepressant treatments, selective serotonin reuptake inhibitors (SSRI), have found that the symptom of anhedonia is not effectively treated, which in turn predicts a longer time to recovery and fewer depression-free days (Shelton & Tomarken, 2001; Spijker, Bijl, De Graaf, & Nolen, 2001). Further, there are reports that SSRIs can in fact contribute to emotional blunting in patients, where experiences, both positive and negative, are flattened (Price, Cole, & Goodwin, 2009). It has therefore been suggested that different pharmacological targets might be needed to adequately treat anhedonia and apathy in depression (Dunlop & Nemeroff, 2007; McCabe, Cowen, & Harmer, 2009; Nutt et al., 2007).

Anhedonia is multi-dimensional, with the anticipatory (appetitive/wanting) and consummatory (hedonic/liking) dimensions being the most widely examined in depression (Frey et al., 2015; McCabe, 2014; Nutt et al., 2007). Affective neuroscience studies of reward 'wanting' and 'liking' have suggested that these psychological processes map onto distinct brain reward systems. For example, studies of pleasure identify hedonic impact in the ventral pallidum, nucleus accumbens and orbitofrontal cortex (OFC) (Berridge & Kringelbach, 2008; Peciña, 2008; Pecina & Berridge, 2005; Pecina, Smith, & Berridge, 2006; Smith & Berridge, 2005; Wheeler & Carelli, 2006), whereas "wanting" or incentive salience is mediated by neural systems that include mesolimbic dopamine projections from the ventral tegmental area to the ventral striatum (Berridge, 2007; Berridge, Robinson, & Aldridge, 2009). Further, dopamine has been shown to be involved in the learning about rewards in prefrontal cortical regions, such as the anterior cingulate cortex and the OFC (Dayan & Balleine, 2002).

Examining the neural correlates of anhedonia in depression, studies have found reduced anticipatory and consummatory responses to reward in the ventral and dorsal striatum and the anterior cingulate (Epstein et al., 2006; Forbes et al., 2009; Pizzagalli et al., 2009;

Smoski et al., 2009; Ubl et al., 2015; Zhang, Chang, Guo, Zhang, & Wang, 2013), with increased activity to the anticipation of gains in the anterior cingulate (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008). Unfortunately few studies investigate the separate dimensions of anhedonia within the same task, which may account for overlapping regions activated across studies in depression (Treadway & Zald, 2011; Zhang et al., 2013). Recent behavioural evidence suggests impairments in the amount of effort expended for rewards in depressed patients (Sherdell, Waugh, & Gotlib, 2012; Treadway, Bossaller, Shelton, & Zald, 2012; Yang et al., 2014), suggesting another possible conceptual dimension of anhedonia needing further investigation. How effort expenditure might map onto neural processes in depression is as yet unclear.

Studies examining the neural response to aversive stimuli in depression are less consistent, with some finding increased responses in regions such as the amygdala (Knutson & Greer, 2008; Sheline et al., 2001; Surguladze et al., 2004), whilst others find reduced/blunted responses in the amygdala and lateral OFC (Bylsma, Morris, & Rottenberg, 2008; Luking, Neiman, Luby, & Barch, 2015; McCabe et al., 2009). However, blunted responses to both reward and aversion fits with the theory of Emotion Context Insensitivity in depression, whereby patients exhibit reduced reactivity to all emotional stimuli (Rottenberg, 2007; Rottenberg, Gross, & Gotlib, 2005).

To assess the neural response to both reward and aversion, we have developed an experimental model that utilizes pleasant and unpleasant sights and tastes. We have previously shown that the SSRI, citalopram, reduced the neural response to the anticipation of reward in the ventral striatum, medial OFC and ventral medial prefrontal cortex (vmPFC) and in the ventral striatum to the taste of the reward (consummatory) (McCabe, Mishor, Cowen, & Harmer, 2010). Citalopram also reduced the neural activation to the anticipation of aversion in the insula and lateral OFC and to the aversive taste in the insula (consummatory) (McCabe et al., 2010). We suggested that this general inhibitory effect might underlie the emotional dampening associated with SSRIs and their alleged inability to effectively treat reward-related deficits in depression (Kumar et al., 2008; Opbroek et al., 2002; Price et al., 2009; Shelton & Tomarken, 2001).

It has been suggested, however, that catecholamine antidepressants like bupropion (dopamine and noradrenaline reuptake inhibitor, DNRI) (Dwoskin, Rauhut, King-Pospisil, & Bardo, 2006; Stahl et al., 2004) might be more efficacious at improving reward-related deficits and apathy in depression and less likely to cause the negative side-effects of sexual dysfunction seen with SSRIs (Argyropoulos & Nutt, 2013; Nutt et al., 2007; Pereira, Arias-Carrión, Machado, Nardi, & Silva, 2014; Shelton & Tomarken, 2001). In fact a recent study examining the human response to erotic images found increased activity in the posterior midcingulate cortex, mediodorsal thalamus, and extended amygdala under bupropion (Abler et al., 2011). However, how the separate dimensions of neural reward and aversion processing (anticipation, effort and consummation) might be affected by bupropion is unknown and is therefore the aim of the current study. To do this we included in our task an anticipatory phase (pleasant or unpleasant cue), an effort phase (button presses to achieve a pleasant taste or to avoid an unpleasant taste) and a consummatory phase (pleasant or unpleasant tastes). We hypothesized that, unlike our previous results with citalopram, bupropion would increase neural responses during anticipation in areas such as the striatum and anterior cingulate cortex. Further, we expected that during the effort phase bupropion would increase the neural activation in regions such as the striatum and prefrontal cortex, as these regions have recently been shown to be activated when working for rewards and avoiding aversion (Delgado, Jou, LeDoux, & Phelps, 2009; Wiers et al., 2014). Additionally, we hypothesized that bupropion would increase neural responses in the striatum and medial OFC during the consummatory phase, given their involvement in hedonic processing. Finally, as with our previous work on the effects of 7 day treatments with antidepressants in healthy volunteers, we expected to find no observable behavioural effects on effort or subjective ratings for each of the stimuli (Harmer, Goodwin, & Cowen, 2009; McCabe et al., 2010).

Materials and Methods

Participants

17 healthy right-handed and Caucasian volunteers (mean 24 years, nine female), were randomized to receive 7 days oral treatment with bupropion (150 mg/day) and 7 days oral treatment with placebo separated by a 2-week washout phase in a double-blind within-groups design. Our previous fMRI study indicated an effect size of d = 0.4 with a mean standard deviation of 0.25 (McCabe et al., 2009), demonstrating that a sample size of 15 would be required to achieve 80% power at an alpha level of 5%. The study was located at the Centre for Neuroscience and Neurodynamics (CINN) in the Department of Psychology at the University of Reading. Volunteers were recruited via advertisement and, after reading study information, provided written consent prior to screening. Ethical approval was obtained from the University of Reading.

The exclusion criteria included current/previous psychiatric disorder (including alcohol or drug dependency) using the DSM-IV Structured Clinical Interview [SCID (Spitzer, Williams, Gibbon, & First, 1992)], pregnancy and any contraindications to MRI and bupropion (including family history of bipolar disorder and seizures/epilepsy). Volunteers were medication-free for the past 3 months (excluding the contraceptive pill) before starting the study and underwent a physical examination. Volunteers had a healthy BMI and their liking and craving for chocolate was measured using a questionnaire (Rolls & McCabe, 2007). Eleven volunteers were non-smokers, four smoked < 1 cigarette a week, one smoked 5 cigarettes per week and one smoked 1-2 cigarettes a day on average. Baseline measures of mood and anhedonia were taken using the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), Snaith-Hamilton Pleasure Scale (Snaith et al., 1995), Fawcett-Clarke Pleasure Capacity Scale (Fawcett, Clark, Scheftner, & Gibbons, 1983), Temporal Experience of Positive Mood (Gard, Kring, Gard, Horan, & Green, 2007) and Behavioral Inhibition/Activation Scales (Carver & White, 1994). Given that we use taste stimuli, including chocolate, volunteers also completed the Eating Attitudes Questionnaire (Garner, Olmsted, Bohr, & Garfinkel, 1982) to assess eating attitudes.

Experimental design

The study used a double blind, within-subjects, counterbalanced, crossover design. Volunteers received 7 days (1 tablet each morning) of bupropion treatment (150mg/day) and 7 days of placebo treatment, separated by a 2-week washout phase. Treatment order was randomised, with 9 volunteers receiving bupropion first and 8 receiving placebo first. A 150 mg/day dose was selected given that bupropion demonstrates clinical efficacy at 150mg/day (Reimherr, Cunningham, Batey, Johnston, & Ascher, 1998) and has previously been shown to alter neural activity to pleasurable stimuli in healthy volunteers after 7 days (Abler et al., 2011). Volunteers underwent an fMRI scan on the 7th day of each treatment at approx. 3 hrs after last dose. One volunteer had a scan after 6 days treatment (drug) due to experiencing adverse side-effects. Medication was provided by the Oxford Health NHS Foundation Trust and the Royal Free London NHS Foundation Trust. Participants were asked to not consume chocolate for 24 hours prior to scanning and were allowed only one caffeinated drink on the scan morning. Before scans, volunteers completed the Patient Rated Inventory of Side Effects (PRISE: Sequenced Treatment Alternatives to Relieve Depression) to record any adverse side-effects. Mood was measured before and after scans using the befindlichkeit scale of mood and energy (Von Zerssen, Strian, & Schwarz, 1974) and a mood visual analogue scale (VAS).

The task was adapted from (McCabe et al., 2010) to include an effort phase (Figure S1). The task (40 trials) had 4 conditions based on the trial type (reward/aversive) and its level of difficulty (easy/hard). Trial type was cued by a visual stimulus (chocolate picture or a picture of a mouldy drink, 2 sec, anticipatory phase), which indicated either to work to win the chocolate taste or to avoid the unpleasant taste. Difficulty was determined by the amount of effort required to complete the effort phase (easy = 24, hard = 45 button presses). The effort phase, required volunteers to press a button as fast as possible (< 6 sec) to move a bar towards the pleasant chocolate picture (reward) and away from the unpleasant mouldy picture (aversive), allowing enough time to complete easy trials but not hard. A taste was then delivered (consummatory phase) based on performance. If on reward trials volunteers were successful they received the taste (5 sec delivery and 2 sec swallow cue) of chocolate and if not they received the tasteless solution. If on aversive trials volunteers were successful they received the tasteless solution and if not they

received the unpleasant taste. A grey image (2 sec) followed by a tasteless rinse was presented at the end of each trial. Each condition was repeated 10 times, chosen by random permutation. Jitters were used for both interstimulus intervals and inter-trial intervals. To sustain effort, 4 trials (2 reward/2 aversive) were longer at 9 sec each. Volunteers also rated 'wanting', 'pleasantness' (+2 to –2) and 'intensity' (0 to +4) on a VAS on each trial (Figure S1).

Stimuli

We used a picture of liquid chocolate (reward), a mouldy drink (aversive) and a grey image (control). The rewarding taste was a Belgian chocolate drink and the aversive taste was a combination of the chocolate drink mixed with beetroot juice, providing a similar texture. The tasteless solution (25 x 10- mol/L KCL and 2.5x10- mol/L NaHCO3 in distilled H2O) was also used as a rinse between trials. This was subtracted from the effects of the other taste stimuli to allow somatosensory and mouth movement effects to be removed (De Araujo, Kringelbach, Rolls, & Hobden, 2003; O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001). Solutions were delivered through three teflon tubes held together by a plastic mouthpiece and connected by a one-way syringe-activated check valve (Model 14044-5, World Precision Instruments, Inc.), allowing 0.5 mL of solution to be manually delivered.

fMRI Scan

The experimental protocol consisted of an event-related interleaved design. A Siemens Magnetom Trio 3T whole body MRI scanner and a thirty-two-channel head coil were used. Multi-band accelerated pulse sequencing (Version number RO12 Center for Magnetic Resonance Research, University of Minnesota, EPI 2D BOLD/SE/DIFF Sequence) was used with an acceleration factor of 6. T2*-weighted echo planner imaging slices were obtained every 0.7 seconds (TR). Imaging parameters were chosen to reduce distortion artefact in the orbitofrontal cortex (Wilson et al., 2002). 54 Axial slices with in-plane resolution of 2.4 x 2.4mm and between plane spacing of 2.4mm were attained. The matrix size was 96 x 96 and the field of view were 230 x 230mm. Acquisition was

performed during task performance, yielding approximately 3500 volumes. An anatomical T1 volume with sagittal plane slice thickness 1mm and in-plane resolution of 1.0 × 1.0 mm was also acquired.

fMRI analysis

Statistical Parametric Mapping (SPM8: http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used to analyze the imaging data. The data was pre-processed using realignment, normalization to the Montreal Neurological Institute (MNI) coordinate system and spatial smoothing with a 6-mm full-width-at-half-maximum Gaussian kernel and global scaling (Collins, Neelin, Peters, & Evans, 1994). The time series at each voxel was low-pass filtered with a hemodynamic response kernel. Time series non-sphericity at each voxel was estimated and corrected for (Friston et al., 2002), and a high-pass filter with a cut-off period of 128 sec was applied.

In the single-event design, a general linear model was then applied to the time course of activation in which stimulus onsets were modelled as single impulse response functions and then convolved with the canonical hemodynamic response function (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation (Worsley et al., 1996), linear contrasts of parameter estimates were defined to test the specific effects of each condition (pleasant/unpleasant cue – grey image and pleasant/unpleasant taste – rinse) with each individual dataset. Voxel values for each contrast resulted in a statistical parametric map of the corresponding t statistic, which was then transformed into the unit normal distribution (SPM z). Movement parameters for each person were added as additional regressors in the 1st level analyses.

Second-level fMRI analyses first examined simple main effects of task with one-sample t-tests for all scans (Table S1). These results were thresholded at p=0.05 uncorrected and

whole-brain cluster corrected [p<0.05 family-wise error (FWE) for multiple comparisons]. To examine the effect of bupropion, the one-way ANOVA within-participants design implemented in SPM8 was used and all data were reported thresholded at p=0.05 uncorrected and whole-brain cluster corrected (p<0.05 FWE for multiple comparisons). Regions of interest, for which we had a priori hypotheses based our previous studies using a similar paradigm in healthy controls, were; ventral striatum [10, 12, -6; -6, 12, -4] (McCabe et al., 2010), caudate [-10, 12, 0; -10, 14, 0] (McCabe et al., 2010), medial OFC [2, 32, -24] (McCabe et al., 2010), vmPFC [8, 56, -12; 2, 44, -14] (McCabe et al., 2009; McCabe et al., 2010) and lateral OFC [46, 34, -6] (McCabe et al., 2010). Peaks within 15mm of these locations and with a cluster threshold of at least 30 contiguous voxels had small volume corrections for multiple comparisons applied (FWE, p<0.05). Plots of contrast estimates were extracted with plots tool in SPM8, and WFU Pick Atlas (http://www.fmri.wfubmc.edu/cms/software) was used to display neural activation, with error bars representing the standard error of the mean. Activation co-ordinates are listed in the stereotactic space of the MNI ICBM 152 brain (Table 2).

Behavioral Data

Data was analyzed using repeated measures ANOVA and employed the Bonferroni correction for multiple comparisons. Where sphericity was violated, the Greenhouse-Geisser correction was utilized. Not-normally distributed data was transformed and reanalyzed. The reanalyzed data did not differ from raw data analysis and thus results are reported using the original data. Caution, however, might be paid to interpretation of the VAS analysis, because a proportion of the data was not normally distributed.

Results

Demographic Details and Mood Ratings

Demographic data (Table 1) indicated that participants had low depression and anhedonia scores, as measured on range of mood and anhedonia questionnaires. Volunteers also scored low on the EAT and reported a strong liking of chocolate. A repeated-measures ANOVA was performed to examine the effect of treatment (bupropion/placebo) and time (pre/post scan) on mood and affect, as measured by the BFS and VAS (Table S2). Results revealed that there was no significant effect of treatment [$F(1,16)=.483$, $p=.497$], time [$F(1,16)=.822$, $p=.378$], treatment by time [$F(1,16)=1.922$, $p=.185$], treatment by VAS [$F(1,16)=2.472$, $p=.084$] or treatment by time by VAS interactions [$F(1,16)=.689$, $p=.545$]. There was also no significant effect of treatment [$F(1,14)=1.61$, $p=.225$] or treatment by time interaction [$F(1,14)=2.176$, $p=.162$] on total BFS scores. However, there was a significant main effect of time on overall BFS score [$F(1,14)=5.879$, $p=.029$].

Table 1. Group Demographic and Psychosocial Measures.

Measure	
Age (years)	24 (4.26)
Ethnicity	100% Caucasian
BMI	23.29 (2.38)
BDI	1.71 (3.14)
FCPS	136.76 (14.48)
SHAPS	20.65 (5.67)
TEPS anticipatory	47.53 (7.75)
TEPS consummatory	37.59 (4.95)
EAT	3.35 (3.71)
BAS Drive	11.06 (2.49)
Fun seeking	11.75 (3.11)
Reward responsiveness	17.53 (1.87)
BIS	20.41 (4.24)
Chocolate craving	5.85 (2.45)
Chocolate liking	8.26 (1.95)
Chocolate frequency (per week)	2.35 (1.91)

Data are means (SD) except for ethnicity, which is percentage.

BMI, Body Mass Index; BDI, Beck Depression Inventory (min-max, 0-40); FCPS, Fawcett Clarke Pleasure Scale (min-max, 36-180); SHAPS, Snaith-Hamilton Pleasure Scale (min-max, 14-56); TEPS, Temporal Experience of Pleasure Scale (min-max: anticipatory, 10-60; consummatory, 8-48); EAT, Eating Attitudes Test (min-max, 0-78); BAS, Behavioral Activation Scale (min-max: drive, 4-16; fun seeking, 4-16; reward responsiveness, 5-20); BIS, Behavioral Inhibition Scale (min-max, 7-28).

Adverse effects

Table S3 reports the number of adverse effects experienced on each treatment, as measured on the PRISE. The most commonly reported adverse effects across both treatment phases were headache (N= 5 per treatment), difficulty sleeping (N= 3 per treatment) and fatigue (N= 3 placebo, N= 5 bupropion). Dizziness (N= 4) was the most commonly reported adverse effect in the bupropion condition that was not reported in the placebo condition.

Subjective Ratings of Stimuli

Volunteers rated the chocolate cue and taste as pleasant and the unpleasant picture and taste as unpleasant (Figure S3). Using repeated-measures ANOVA with Ratings as the first factor with three levels (wanting, pleasantness and intensity), Treatment as the second factor with two levels (bupropion and placebo) and Condition as the third factor with two levels (rewarding and aversive), there was no significant main effect of treatment [$F(1,16)=.867$, $p=.366$] or treatment by condition interaction [$F(1,16)=2.558$, $p=.129$], treatment by rating interaction [$F(1,16)=.109$, $p=.802$] or treatment by rating by condition interaction [$F(1,16)=.701$, $p=.479$].

Behavioral responses

To examine whether there was an effect of treatment on the amount of effort invested into each condition (reward/aversion), repeated-measures ANOVAs were conducted on the average number of button presses made and the average amount of time it took to complete the effort stage (Figure S4). With Treatment (bupropion and placebo) and Condition (reward and aversion) included as factors, it was revealed that volunteers made significantly more button presses on aversive trials ($M=37.69$, $SE = 0.33$) compared to reward trials ($M=37.37$, $SE=0.34$) [$F(1,16)=5.736$, $p=0.029$]. This was independent of treatment, since there was no main effect of treatment [$F(1,16)=.028$, $p=.869$] or treatment by condition interaction [$F(1,16)=.063$, $p=.804$]. Furthermore, although volunteers completed aversive trials ($M=5519.33$ms, $SE=46.43$) quicker than reward trials ($M=5546.57$ms, $SE=45.11$), this was not significant [$F(1,16)=2.106$, $p=.166$], nor

was there a main effect of treatment [$F(1,16)=.023$, $p=.881$] or treatment by condition interaction [$F(1,16)=1.654$, p=.217].

fMRI responses

Table S1 in the Supplementary Material provides a summary of the results for each contrast across all volunteers to indicate the main effect of task. Table 2 provides a summary of the results of the interaction with Treatment.

Main Effect of Task

As expected, the chocolate stimuli activated reward-related areas, such as the ventral striatum, the anterior cingulate and the OFC, whereas the unpleasant stimuli activated regions including the amygdala and lOFC. Both the chocolate taste and unpleasant tastes activated the insula (i.e. the primary taste cortex).

Anticipatory Phase

Relative to the placebo condition, the bupropion condition showed increased BOLD activity in the caudate in response to *both* the pleasant and unpleasant cue. To the pleasant cue, the bupropion condition showed more activity in the pgACC/vmPFC (Fig 1) and lOFC, in comparison to placebo. To the unpleasant cue, the bupropion condition showed more BOLD activity in the vmPFC, relative to placebo.

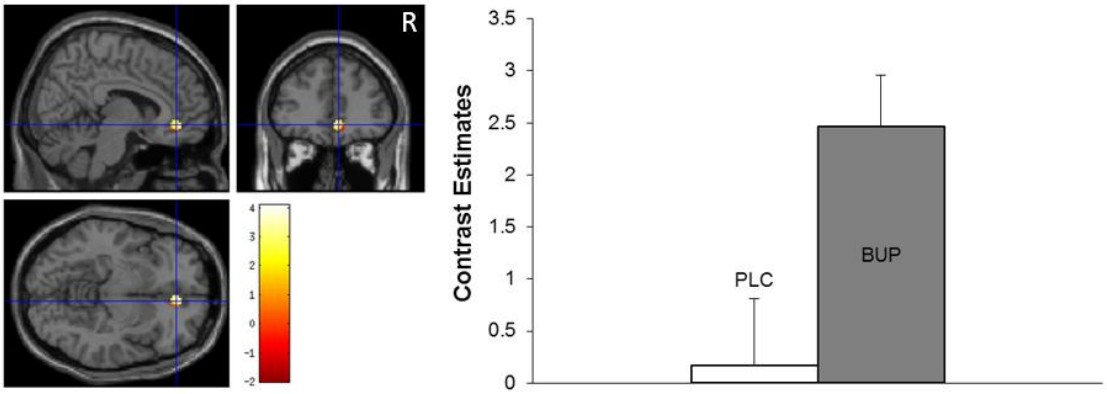

Figure 1. Pleasant cue: left panel, axial, sagittal and coronal image of pregenual anterior cingulate cortex/ventromedial prefrontal cortex pgACC/vmPFC activation compared to placebo (Z=3.33, p=0.02 family-wise error small volume correction for multiple comparisons); right panel, contrast estimates for pgACC centred at 8, 40, -8. Error bars represent the standard error of the mean. PLC, placebo; BUP, bupropion.

Effort Phase

For bupropion there was increased BOLD activity in the caudate, vmPFC (Figure 2), dACC/paracingulate gyrus and putamen for the easy chocolate trials compared to hard chocolate trials, in comparison to placebo. Bupropion also increased BOLD activity in the primary motor cortex and ventral striatum/caudate for the easy unpleasant trials compared to hard unpleasant trials. Bupropion increased BOLD activity in the dorsal anterior cingulate cortex (dACC)/paracingulate gyrus and the superior frontal gyrus for the easy chocolate trials compared to the easy aversive trials, relative to placebo.

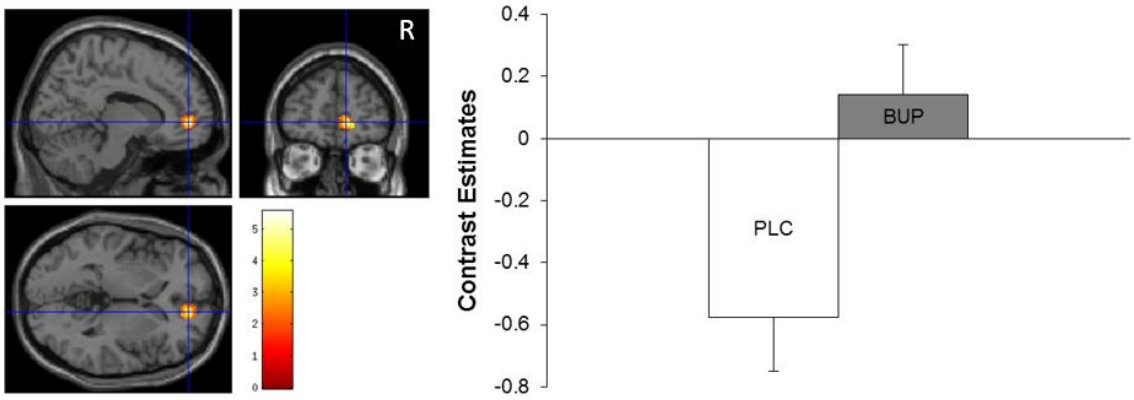

Figure 2. Easy effort chocolate – hard effort chocolate: left panel, axial, sagittal and coronal image of ventromedial prefrontal cortex (vmPFC) activation compared to placebo (Z=4.09, p<0.001 family-wise error whole brain cluster corrected for multiple comparisons); right panel, contrast estimates for vmPFC centred at 12, 50, 0. Error bars represent the standard error of the mean. PLC, placebo; BUP, bupropion.

Consummatory Phase

Bupropion increased BOLD activity in the mOFC to *both* the pleasant (Figure 3) and unpleasant tastes. Bupropion increased BOLD activity in the amygdala (Figure 4) and ventral striatum for the unpleasant taste relative to the placebo condition. Bupropion also reduced BOLD activity for the pleasant taste in the caudate, relative to the placebo condition.

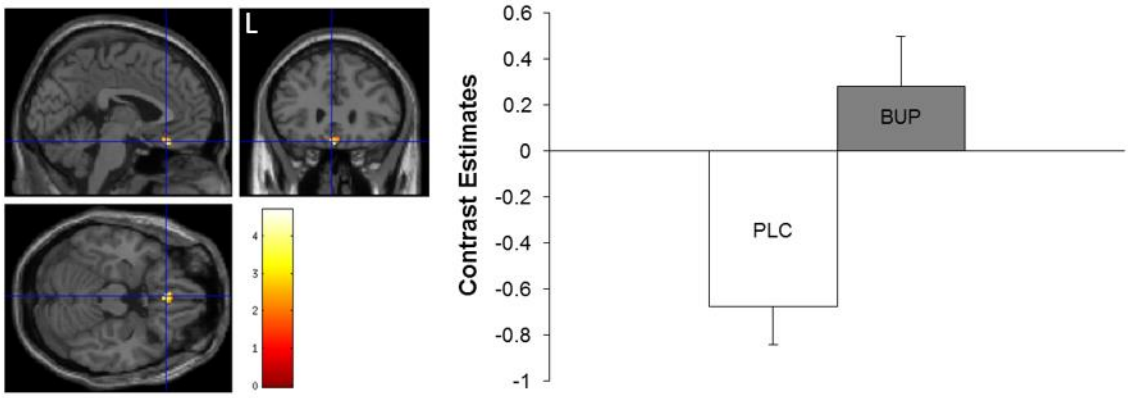

Figure 3. Chocolate taste: left panel, axial, sagittal and coronal image of medial orbitofrontal cortex (mOFC) activation compared to placebo (Z=3.67, p=0.005 family-wise error small volume correction for multiple comparisons); right panel, contrast estimates for mOFC centred at -2, 28, -20. Error bars represent the standard error of the mean. PLC, placebo; BUP, bupropion.

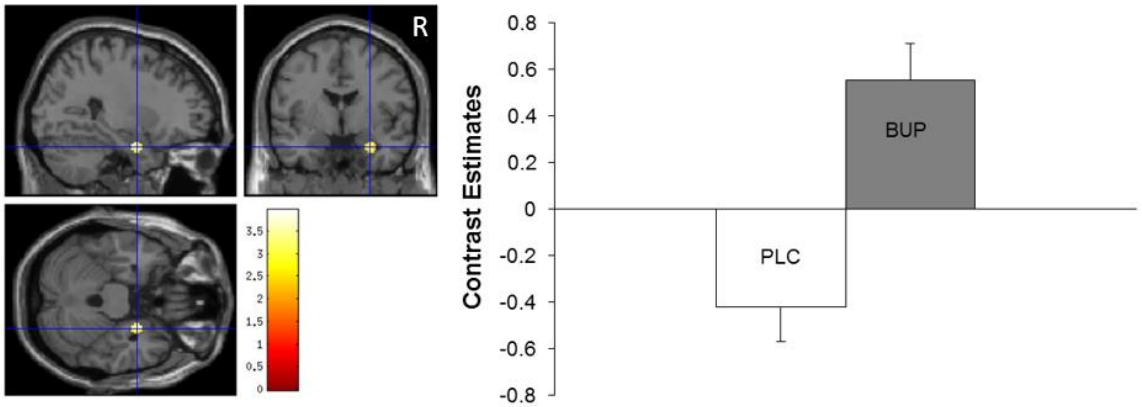

Figure 4. Unpleasant taste: left panel, axial, sagittal and coronal image of amygdala activation compared to placebo (Z=3.26, p=0.014 family-wise error whole brain cluster corrected for multiple comparisons); right panel, contrast estimates for amygdala centred at 28,-2,-26. Error bars represent the standard error of the mean. PLC, placebo; BUP, bupropion.

Table 2. Regions showing significant effect of treatment on each condition.

	MNI coordinates				
Brain Region	X	Y	Z	Z score	Significance (*p* Value)
Anticipatory					
Chocolate cue: bupropion > placebo					
lOFC	-42	44	-12	4.11	0.001*
Caudate	-6	16	6	3.73	0.007*
pgACC/vmPFC	8	40	-8	3.33	0.02*
Unpleasant cue: bupropion > placebo					
vmPFC	-12	48	0	3.98	0.003*
Caudate	-4	16	6	3.61	0.01*
Effort					
Easy chocolate – hard chocolate: bupropion > placebo					
vmPFC	12	50	0	4.09	<0.001
Caudate	10	6	2	3.97	<0.001
Putamen	-14	8	0	3.45	<0.001
dACC/paracingulate gyrus	-6	28	42	3.45	<0.001
Easy unpleasant – hard unpleasant: bupropion > placebo					
Ventral striatum/caudate	-12	20	-6	3.42	<0.001
Primary motor cortex	-38	-8	50	4.06	<0.001

Easy chocolate – easy unpleasant: bupropion > placebo					
Superior frontal gyrus	-24	32	46	4.30	<0.001
dACC/paracingulate gyrus	6	28	42	4.10	<0.001
Consummatory					
Chocolate taste: bupropion > placebo					
mOFC	-2	28	-20	3.67	0.005*
Chocolate taste: placebo > bupropion					
Caudate	-2	8	10	4.07	<0.001
Unpleasant taste: bupropion > placebo					
mOFC	-2	28	-20	3.76	0.014
Amygdala	28	-2	-26	3.26	0.014
Ventral striatum	12	6	-6	3.11	0.014

MNI, Montreal Neurological Institute; lOFC, lateral orbitofrontal cortex; pgACC, pregenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; dACC, dorsal anterior cingulate; mOFC, medial orbitofrontal cortex; Mid OFC, middle orbitofrontal cortex; Cing, cingulate.

Data thresholded at p=0.05 uncorrected.

p values: Family-wise error whole brain fully corrected or *family-wise error small volume correction $p<0.05$.

Discussion

The aim of this study was to examine the effects of 7 days treatment with bupropion on the neural response to three phases of reward and aversion processing (anticipation, effort and consummation) in healthy volunteers. We found that bupropion increased neural responses during the anticipation, effort to achieve/avoid and the consummation of rewarding and aversive tastes. The effects on reward are consistent with the proposal that bupropion may significantly improve outcomes for depressed patients with predominant symptoms of decreased pleasure, interest and energy (Corcoran, Wong, & O'Keane, 2004; Nutt et al., 2007). Further, bupropions ability to increase neural responses during anticipation, avoidance and consummation of aversive stimuli may be additionally beneficial for patients experiencing blunted affect in depression whereby reduced reactivity to positive and negative stimuli is predominant (Rottenberg, 2007; Rottenberg et al., 2005).

Specifically we found that bupropion increased activity during the anticipation phase (pleasant and unpleasant cues) in the vmPFC and the caudate, with increased lateral OFC to the pleasant cue. These regions are recruited during anticipation of reward (Kim, Shimojo, & O'doherty, 2010; Sescousse, Caldú, Segura, & Dreher, 2013) and found blunted to the anticipation of reward in patients with depression (McCabe et al., 2009; Price & Drevets, 2010). We also found that the caudate was increased during the anticipation phase (pleasant and unpleasant cues) in the bupropion group compared to placebo. The caudate, which has been previously shown to be activated during the anticipation of pleasant and unpleasant stimuli in healthy volunteers (Gerdes et al., 2010), has been found hypoactive during the anticipation of reward in people with depression (Forbes et al., 2009; Smoski et al., 2009; Zhang et al., 2013). Thus bupropions ability to modulate activation in these regions during anticipation of reward and aversion might be a mechanism by which catecholaminergic medications are less likely to cause emotional blunting in depression compared to SSRI medications (Argyropoulos & Nutt, 2013; Bylsma et al., 2008; Nutt et al., 2007; Shelton & Tomarken, 2001).

During the effort phase, we found that there was more neural activity under hard trials than easy in the placebo group (Figure S2). We found that the activity under easy trials

was potentiated by bupropion, in the striatum, vmPFC (Figure 2) and the dACC/motor areas, relative to placebo. Given the previous work showing that these regions are implicated in various processes involved in reward processing including motor performance (Liljeholm & O'Doherty, 2012; Scholl et al., 2015)and in the avoidance of aversion (Kerr, McLaren, Mathy, & Nitschke, 2012), its perhaps not surprising that bupropion enhanced this neural activity during effort expenditure to achieve reward and avoid aversion.

During the consummatory phase we found that bupropion, compared to placebo, increased neural activity for both pleasant and unpleasant tastes in the mOFC. Our results are consistent with the literature indicating the involvement of the mOFC in hedonic experiences in humans and animals (Kringelbach, 2010; Peters & Büchel, 2010; Scott et al., 2005). Further, our previous study in those recovered from depression found reduced activity to the taste of chocolate (possible trait marker) in a similar subgenual/mOFC region to that enhanced by bupropion in this current study (McCabe et al., 2009). Of note, a study found reduced activations in depressed patients to both positive and negative outcomes in the striatum (Pizzagalli et al., 2009), which is of interest given that we find enhanced striatal activation to the unpleasant taste under bupropion in our task. Taken together our results suggest that bupropion may be beneficial at increasing the neural deficits to both positive and negative consummatory stimuli in depressed patients who report blunted affect.

As expected, there was no significant treatment effect on the amount of effort invested in the task or on the subjective reports of pleasantness, wanting and intensity for each of the stimuli. This is similar to our previous studies with acute pharmacological challenges in healthy volunteers and suggests that enhanced neural processing of reward/aversion after 7 days treatment does not necessarily become the subject of conscious awareness, although it could still presumably influence behavior (Horder, Harmer, Cowen, & McCabe, 2010; McCabe et al., 2010; Tudge, Williams, Cowen, & McCabe, 2015). Perhaps there is also a ceiling effect as volunteers are all healthy and do not have deficits in their ability to complete the effort component or to experience the tastes. However,

how bupropion might affect these processes in studies with larger sample sizes and in depressed patients remains to be elucidated.

To conclude, we suggest a potential mechanism of beneficial antidepressant drug action of bupropion that consists of enhancing the neural activation to reward and aversion during anticipation, effort and consummation. This profile of activity in turn could promote reward-seeking and aversive-avoidant behaviors in patients with depression, whereby a lack of drive to actively seek and experience rewards is coupled with a lack of drive to actively avoid negative experiences. Our results also support the notion that non-serotonergic antidepressants may play an important role specifically for patients that have a blunted emotional affect and this fits with the Emotion Context Insensitivity theory of depression (Rottenberg et al., 2005). Future research on the effects of bupropion on anticipation, effort and consummation of reward and aversion processing in depressed patients are encouraged to explore this notion further.

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Conflict of interest

Dr. McCabe has acted as a consultant to P1Vital, Givaudan, GWpharma, the British Broadcasting Company (BBC) and Channel 4. Zola Dean, Dr. Stefanie Horndasch and Dr. Panagiotis Giannopoulos report no biomedical financial interests or potential conflicts of interest.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Supplementary information is available at the Psychological medicine website

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5. Paper 3: Increased Neural Response during the Anticipation and Effort to Avoid Aversion, but not Reward, Following Agomelatine Treatment.

Manuscript in preparation.

Title:

Increased Neural Response during the Anticipation and Effort to Avoid Aversion, but not Reward, Following Agomelatine Treatment

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Abstract

Background

We have previously found that a selective serotonin reuptake inhibitor reduces, whereas a dopamine and noradrenaline reuptake inhibitor increases, neural activity to reward and aversion, in healthy volunteers. Agomelatine increases dopamine and noradrenaline via disinhibition and may be more beneficial for treating anhedonia than serotonergic antidepressants. However, how agomelatine affects neural activity to reward and aversion remains to be examined.

Methods

Eighteen healthy volunteers (mean age 21 years, 12 female) received 7 days agomelatine (25 mg/day) and 7 days placebo treatment, in a randomized, double-blind, crossover design. Using functional magnetic resonance imaging, we examined how agomelatine affected neural activity to pleasant and unpleasant cues (anticipation), whilst button pressing to obtain reward and avoid aversion (effort), and to pleasant and unpleasant tastes (consummation). We also explored how subjective experiences (wanting and pleasantness) modulated neural activity.

Results

Compared to placebo, agomelatine increased activity during the anticipation of aversion in the pregenual anterior cingulate cortex/ventral medial prefrontal cortex (pgACC/vmPFC). During the effort phase, there was more ACC activity after agomelatine treatment when avoiding aversion, relative to obtaining reward. Agomelatine reduced activity in the pre/postcentral gyrus to the unpleasant taste. Agomelatine did not affect activity during reward processing.

Conclusions

Our results are the first to suggest that agomelatine can alter neural activity during the anticipation, effort to avoid, and consummation of aversive stimuli. Modifying activity to aversion without dampening responses to reward, may help explain why agomelatine is effective at improving anhedonia and emotional blunting.

Introduction

Only 25-55% of depressed patients respond to current antidepressant treatments (Nutt et al., 2007; Trivedi et al., 2006). This is potentially due the complex symptomology and heterogeneous nature of Major Depressive Disorder (MDD) and thus, not all symptoms are being effectively targeted (Argyropoulos & Nutt, 2013). Selective serotonergic re-uptake inhibitors (SSRIs) are thought to exert beneficial effects by reducing negative/aversive information processing (Harmer, Duman, & Cowen, 2017). However, SSRIs are criticized for being less effective treatments for anhedonia, underpinned by dysfunctional reward processing (Argyropoulos & Nutt, 2013).

SSRIs might not be the most effective treatments for anhedonia as they do not directly enhance dopamine (Blier & Briley, 2011; Dunlop & Nemeroff, 2007). In fact, there is even some evidence to suggest that some SSRIs inhibit dopaminergic pathways via stimulating 5-HT_{2C} receptors (Di Matteo, De Blasi, Di Giulio, & Esposito, 2001; Dremencov, El Mansari, & Blier, 2009; Prisco & Esposito, 1995). As a result, it has been proposed that medications that increase catecholamines, such as dopamine and noradrenaline, may be more effective at improving anhedonia in MDD (Argyropoulos & Nutt, 2013).

To investigate neural activity to reward and aversion, we have developed an experimental model measuring both the anticipation and consummation of a pleasant and unpleasant taste. We have previously shown that those at risk of MDD have blunted neural activity to chocolate reward (McCabe, Cowen, & Harmer, 2009; McCabe, Woffindale, Harmer, & Cowen, 2012), and that this correlates with MDD symptoms and anhedonia in adolescents, compared to controls (Rzepa, Fisk, & McCabe, 2017). Furthermore, we have previously shown that the SSRI, citalopram, reduces brain activity during reward *and* aversion processing in healthy volunteers (McCabe, Mishor, Cowen, & Harmer, 2010). We suggest that this overall reduction might explain reports of emotional-blunting during SSRI treatment (Bolling & Kohlenberg, 2004; Goodwin, Price, De Bodinat, & Laredo, 2017; Price & Goodwin, 2009).

Since catecholamine-enhancing antidepressants are theorized to be more effective treatments for anhedonia (Argyropoulos & Nutt, 2013), we recently examined the dopaminergic and noradrenergic reuptake inhibitor, bupropion. We adapted our task to measure effort expenditure to obtain reward and to avoid aversion, as physical effort might be a better indicator of motivation. We found that bupropion increased activity in the caudate and pregenual anterior cingulate/ventral medial prefrontal cortex (pgACC/vmPFC) during both reward and aversion anticipation. During the effort phase, bupropion increased activity in the vmPFC, striatum, dorsal ACC and primary motor cortex during easy versus hard trials. Further, bupropion increased activity in the medial orbitofrontal cortex (mOFC) during reward and aversion consummation and in the amygdala, ventral striatum and vmPFC during aversion consummation. As was expected, these effects were the opposite to those seen with citalopram (McCabe et al., 2010), and thus we suggest that bupropion might be useful for patients with blunted affect i.e. reduced reactivity to both positive and negative events (Dean, Horndasch, Giannopoulos, & McCabe, 2016).

Agomelatine is an atypical antidepressant that is an agonist at melatonin (MT_1 and MT_2) receptors and an antagonist at 5-HT_{2B} receptors. However agomelatine also increases dopamine and noradrenaline in the PFC by disinhibiting 5-HT_{2C} receptors (Chenu, El Mansari, & Blier, 2013; Millan, Brocco, Gobert, & Dekeyne, 2005; Millan et al., 2003; Stahl, 2007). Crucially, whereas SSRIs inhibit the dopaminergic mesocorticolimbic pathway by stimulating 5-HT_{2C} receptors, possibly underlying their inability to treat anhedonia, agomelatine prevents activity at these receptors (Di Matteo et al., 2001; Dremencov et al., 2009; Prisco & Esposito, 1995). Indeed, it has been demonstrated that 5-HT_{2C} antagonism can improve, and prevent the detrimental effects of 5-HT_{2C} agonists on, reward-motivated behaviour in rodents (Bailey et al., 2016; Cunningham et al., 2011; Higgins et al., 2013; Simpson et al., 2011). Consistent with this, agomelatine has been found to improve anhedonia and emotional blunting, and may be superior at doing so compared to venlafaxine and SSRIs (Corruble, de Bodinat, Belaïdi, & Goodwin, 2013; De Berardis et al., 2013; Di et al., 2011; El Yacoubi, Dubois, Gabriel, Mocaër, &

Vaugeois, 2011; Gargoloff et al., 2016; Gorwood et al., 2015; Martinotti et al., 2012; Papp, Gruca, Boyer, & Mocaër, 2003).

There is also evidence to suggest that agomelatine is effective at alleviating symptoms such as low mood and anxiety. For example, various trials and a recent meta-analysis have demonstrated the efficacy of agomelatine at improving depression symptoms (Kennedy & Emsley, 2006; Loo, Hale, & D'haenen, 2002; Stahl et al., 2010; Taylor, Sparshatt, Varma, & Olofinjana, 2014). There is also evidence using both humans and animals to suggest that agomelatine has anxiolytic effects (Loo et al., 2002; Millan et al., 2005; Papp, Litwa, Gruca, & Mocaër, 2006; Stein, Picarel-Blanchot, & Kennedy, 2013). Moreover, 7 days agomelatine treatment in healthy volunteers reduced the recognition of sad facial expressions and startle responses to unpleasant images, suggesting attenuated aversion processing (Harmer et al., 2011). Taken together, this suggests that agomelatine is effective at improving negative affective symptoms, as well as positive affective symptoms.

However, how agomelatine affects reward and aversion processing in the human brain is unknown. Therefore, the aim of this study was to examine the neural effects of 7 days agomelatine treatment in healthy volunteers using our reward/aversion model, with anticipatory, effort and consummatory phases. We hypothesized that, similar to bupropion (Dean et al., 2016), but unlike citalopram (McCabe et al., 2010), agomelatine would enhance activity during reward anticipation, effort and consummation. In line with the evidence suggesting reduced aversion processing during agomelatine treatment, we expected that agomelatine would reduce neural activity during reward anticipation, effort and consummation. More specifically, we expected activity in the striatum, ACC and PFC to be altered during anticipation and effort, and activity in the striatum and mOFC to be altered during consummation (Dean et al., 2016; Delgado, Jou, LeDoux, & Phelps, 2009; McCabe et al., 2010; Wiers et al., 2014). Given that we have data from examining bupropion using the same task in healthy volunteers; we also directly compared the effects of agomelatine with bupropion. Furthermore, since we collected trial-by-trial

subjective measures (including wanting and liking), we also examined how brain activity at each phase was modulated by subjective experience.

Methods and Materials

Participants

Twenty-one healthy volunteers were recruited. However, one volunteer was excluded due to developing a rash and another for being an outlier on the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), leaving eighteen participants (mean age 21 years, 12 female). Our previous fMRI study indicated an effect size of d = 0.4 with a mean standard deviation of 0.25 (McCabe et al., 2009), demonstrating that a sample size of 15 would be required to achieve 80% power at an alpha level of 5%. Volunteers were randomized to receive 7 days oral treatment with agomelatine (25mg/day) and 7 days oral treatment with placebo, separated by a 2-week washout phase. The study was located at the Centre for Neuroscience and Neurodynamics (CINN) in the Department of Psychology at the University of Reading. Volunteers were recruited via advertisement and, after reading study information, they provided written consent, prior to screening. Ethical approval was obtained from the University of Reading and South-Central Berkshire B Research Ethics committee.

The exclusion criteria was current/previous psychiatric disorder determined using the DSM-IV Structured Clinical Interview (SCID (Spitzer, Williams, Gibbon, & First, 2004)), the use of psychoactive medication, pregnancy, and any contraindications to magnetic resonance imaging (MRI) or agomelatine (including current/past hepatic or renal impairment). Since agomelatine increases liver enzymes, volunteers provided a blood sample and were excluded if levels of aspartate transaminase and alanine transaminase were not within the normal range, at the time of screening. Volunteers underwent a physical examination, had a healthy BMI and were non-smokers. Baseline measures of mood and anhedonia were taken at screening, using the BDI (Beck et al., 1961), Temporal Experience of Pleasure Scale (TEPS) (Gard, Kring, Gard, Horan, & Green, 2007) and Behavioral Inhibition/Activation Scales (Carver & White, 1994). Given that we use taste stimuli, including chocolate, volunteers also completed the Eating Attitudes Questionnaire (Garner, Olmsted, Bohr, & Garfinkel, 1982) and chocolate liking questionnaire (Rolls & McCabe, 2007).

Experimental design

The study used a randomized, double blind, placebo-controlled, crossover design. Volunteers received 7 days (one tablet each evening) agomelatine treatment (25mg/day) and 7 days placebo treatment, separated by a 2-week washout phase. Treatment order was randomized. A 25mg/day dose was selected based on its clinical efficacy (Loo et al., 2002; Stahl et al., 2010), which has previously been shown to improve low mood and memory for positive self-referential words in healthy volunteers after 7 days (Harmer et al., 2011). Volunteers underwent an fMRI scan, on the 8th morning after starting the 7 days treatment, at 9.00-11.00am. One volunteer had a scan after 6 days treatment (agomelatine) due to forgetting to take one pill. Medication was provided by the Oxford Health NHS Foundation Trust and the Royal Free London NHS Foundation Trust. Participants were asked to not consume chocolate for 24 hours prior to scanning. After the treatment and before the scan, volunteers completed the Patient Rated Inventory of Side Effects to record any adverse side-effect (PRISE) (Rush et al., 2004). Mood and state anhedonia was measured before and after treatment using the Befindlichkeit Scale of mood and energy (BFS) (von Zerssen, Strian, & Schwarz, 1974) and a mood visual analogue scale (VAS). Volunteers also completed the state TEPS measure on the morning of each scan (Gard et al., 2007).

The task (36 trials) was split into 4 conditions based on the trial type (reward/aversive) and its level of difficulty (easy/hard) presented in a pseudorandom permutation. Trial type was cued by a visual stimulus (chocolate picture or a picture of a mouldy drink, 2 sec, anticipatory phase), which indicated whether they were working to win the chocolate taste or to avoid the unpleasant taste. Difficulty was determined by the amount of effort required to complete the effort phase (easy = 23, hard = 46 button presses). The effort phase, required volunteers to press a button as fast as possible (< 6 sec) to move a bar towards the pleasant chocolate picture (reward) or away from the unpleasant mouldy picture (aversive), allowing enough time to complete easy trials but not hard. A taste was then delivered (consummatory phase) based on performance. If on reward trials volunteers were successful they received the taste (5 sec delivery and 2 sec swallow cue) of chocolate and if not they received the tasteless solution. If on aversive trials volunteers were successful they received the tasteless solution and if not they received the unpleasant

taste. A grey image (2 sec) followed by a tasteless rinse was presented at the end of each trial. Jittering were used for both interstimulus intervals and inter-trial intervals. To sustain effort, 2 trials (1 reward/1 aversive) were longer at 9 sec each. Volunteers also rated 'wanting', 'pleasantness' (+2 to –2) and 'intensity' (0 to +4) on a VAS on each trial (Figure S1).

Stimuli

We used a picture of liquid chocolate (reward), a mouldy drink (aversive) and a grey image (control). The rewarding taste was a Belgian chocolate drink and the aversive taste was a combination of the chocolate drink mixed with beetroot juice, providing a similar texture. The tasteless solution (25 x 10^{-} mol/L KCL and 2.5x10^{-} mol/L $NaHCO_3$ in distilled H_2O) was also used as a rinse between trials. This was subtracted from the effects of the other taste stimuli to allow somatosensory and mouth movement effects to be removed (De Araujo, Kringelbach, Rolls, & Hobden, 2003; O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001). Solutions were delivered through three Teflon tubes held together by a plastic mouthpiece and connected by a one-way syringe-activated check valve (Model 14044-5, World Precision Instruments, Inc.), allowing 0.5 mL of solution to be manually delivered.

fMRI Scan

An event-related interleaved design and Siemens Magnetom Trio 3T whole-body MRI scanner and a 32-channel head coil were used. Two volunteers were scanned after the MRI scanner was upgraded to a Siemens MAGNETOM Prisma 3T whole-body MRI scanner, but scanning parameters were kept consistent across the two systems. Multi-band accelerated pulse sequencing (version no. RO12, Center for Magnetic Resonance Research, University of Minnesota, USA, EPI 2D BOLD/SE/DIFF Sequence) was used with an acceleration factor of 6. T2*-weighted echo planner imaging slices were obtained every 0.7 s (TR). Fifty-four axial slices with in-plane resolution of 2.4 × 2.4 mm and between-plane spacing of 2.4 mm were attained. The matrix size was 96 × 96 and the field of view was 230 × 230 mm. Acquisition ~3500 volumes. An anatomical T1 volume

with sagittal plane slice thickness of 1 mm and in-plane resolution of 1.0 × 1.0 mm was also acquired.

fMRI analysis

Similar to our previous data analyses (Dean et al., 2016), we used Statistical Parametric Mapping (SPM8) for realignment and normalization to the Montreal Neurological Institute (MNI) coordinate system and spatial smoothing with a 6-mm full-width-at-half-maximum Gaussian kernel (Collins, Neelin, Peters, & Evans, 1994). The time series at each voxel was low-pass filtered with a hemodynamic response kernel. Time series non-sphericity at each voxel was estimated and corrected for (Friston et al., 2002), with a high-pass filter with cut-off period of 128 sec.

In the single-event design, a general linear model was then applied to the time course of activation in which stimulus onsets were modeled as single impulse response functions and then convolved with the canonical hemodynamic response function (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation (Worsley, Marrett, Neelin, Friston, & Evans, 1996), linear contrasts of parameter estimates were defined to test the specific effects of each condition (pleasant/unpleasant cue – grey image, pleasant/unpleasant taste – rinse, reward/aversive effort hard-effort easy) with each individual dataset. Voxel values for each contrast resulted in a statistical parametric map of the corresponding *t* statistic (transformed into the unit normal distribution (SPM *z*)). Movement parameters and parameters of no interest (such as the onsets of the VAS displays) were added as additional regressors.

Second-level fMRI analyses first examined simple main effects of task with one-sample *t*-tests for all subjects, thresholded at $p \leq 0.001$ uncorrected and whole-brain cluster corrected (family-wise error (FWE) for multiple comparisons). To examine the effect of agomelatine compared to placebo, the one-way ANOVA within-participants design implemented in SPM8 was used and results thresholded at $p \leq 0.05$ uncorrected and whole-

brain cluster corrected (FWE for multiple comparisons). To examine the effects of agomelatine compared to bupropion, the paired *t*-test design was used, with age and gender added as covariates of no interest. Results were thresholded at $p \leq 0.01$ uncorrected and whole-brain cluster corrected (FWE for multiple comparisons). We also report results from a region of interest (ROIs) analysis, using Wake Forest University (WFU) PickAtlas toolbox (http://www.fmri.wfubmc.edu/cms/software) thresholded at $p=0.05$ uncorrected with *p* values for peak voxels being FWE corrected for multiple comparisons within the ROI. We created a single mask containing ROI spheres (subcortical: 6mm; cortical: 8mm) for the following 5 regions, based on our previous studies; ventral striatum [10, 12, -6; -6, 12, -4] (McCabe et al., 2010), caudate [-10, 12, 0; 10, 14, 0] (McCabe et al., 2010), medial OFC [2, 32, -24] (McCabe et al., 2010), vmPFC [8, 56, -12; 2, 44, -14] (McCabe et al., 2009; McCabe et al., 2010) and lateral OFC [46, 34, -6] (McCabe et al., 2010). Results with a *Z*-score of ≥3.00 were reported. For hard versus easy contrasts, the average time difference to complete these trials were included as an additional covariate at the second level. Plots of contrast estimates were extracted with plots tool in SPM8 and WFU PickAtlas was used to display neural activation, with error bars representing the standard error of the mean. Activation co-ordinates are listed in the stereotactic space of the MNI ICBM 152 brain.

A parametric modulation approach was used to determine whether brain activity covaried with behavioural data, collected on a trial-by-trials basis. Four models were performed. In models 1 and 2, wanting ratings, the number of button presses, and pleasantness ratings were entered as parametric modulators during the anticipation, effort, and consummation phase, respectively. In models 3 and 4, on the other hand, wanting ratings were entered as parametric modulators during the effort phase (and not the anticipation phase) and pleasantness ratings were entered as parametric modulators during the consummation phase. Wanting ratings were assessed using raw values (models 1 and 3) and absolute values (models 2 and 4), to track regions modulated by valence and incentive, respectively. Movement parameters and covariates of no interest (e.g. the onsets of the VAS displays) were added as additional regressors. In second-level analyses, one-sample *t*-tests were performed to determine what regions covaried with the respective modulator after drug and placebo treatment, separately. Results were thresholded at $p \leq 0.01$

uncorrected and whole-brain cluster corrected (FWE for multiple comparisons). Paired samples *t*-tests were then conducted to identify regions that covaried more strongly with a given modulator, under drug versus placebo. Results were thresholded at $p \leq 0.05$ uncorrected and whole-brain cluster corrected (FWE for multiple comparisons). We also performed ROI analyses, based on our results comparing agomelatine versus placebo, during reward and aversion anticipation, effort and consummation. This was achieved by creating a single mask for each phase (anticipation, effort and consummation) containing spheres around the peak voxels of suprathreshold clusters to agomelatine versus placebo (subcortical: 6mm; cortical: 8mm). Results were thresholded at $p=0.05$ uncorrected with *p* values for peak voxels being FWE corrected for multiple comparisons within the ROI.

To examine for global hemodynamic changes caused by agomelatine, a paired *t*-test comparing agomelatine vs placebo was performed in a ROI to the grey image, thresholded at $p=0.05$ uncorrected with *p* values for peak voxels being FWE corrected for multiple comparisons within the ROI. The ROI was identified by performing a one-sample *t*-test on all subjects under placebo to the grey image, thresholded at $p=0.05$ uncorrected and whole-brain cluster corrected (FWE for multiple comparisons). The most significantly active cluster was saved and exported as a ROI using Marsbar software (Brett, Anton, Valabregue, & Poline, 2002).

Behavioural Data

The differences between state TEPS scores collected on the morning of each scan was analysed using a paired samples t-test. The remaining data were analysed using repeated measures ANOVAs and employed the Bonferroni correction for multiple comparisons. Where sphericity was violated, the Greenhouse-Geisser correction was utilized.

Results

Demographic Details and Mood Ratings

One volunteer failed to complete some questionnaires leaving N=17 for the baseline measures. Demographic data (Table 1) indicated that participants had low depression and anhedonia scores. Volunteers also scored low on the EAT and reported a strong liking of chocolate. A repeated-measures ANOVA was performed to examine the effect of treatment (agomelatine/placebo) and time (pre/post-treatment) on mood and affect, as measured by the BFS and VAS (Table S1). Results revealed that there was no significant effect of treatment [F(1,17)=2.185, p=.158], time [F(1,17)=.583, p=.456], treatment by time [F(1,17)=.036, p=.851], treatment by VAS [F(2.502,42.531)=.705, p=.530] or treatment by time by VAS interactions [F(3.262,2.689)=2.92, p=.070]. One participant's data for the BFS was excluded, due to missing items on the pre-treatment measure. There was also no significant effect of treatment [F(1,16)=1.845, p=.193], time [F(1,16)=.225, p=.642] or treatment by time interaction [F(1,16)=.196, p=.664] on BFS scores or significant treatment effect on state TEPs scores [t(17)=.965, p=.348].

Table 1. Group Demographic and Psychosocial Measures.

Measure	
Age (years)	20.78 (3.41)
Gender	12 female, 6 male
Ethnicity	12 Caucasian; 2 Black; 1Asian; 1 Chinese; 1 Black/Irish; 1Middle Eastern
BMI	22.65 (1.74)
BDI	1.78 (2.16)
TEPS anticipatory	52.06 (39.65)
TEPS consummatory	39.65 (6.38)
EAT	4.59 (3.73)
BAS Drive	15.60 (2.69)
Fun seeking	17.00 (2.17)
Reward responsiveness	23.00 (1.69)
BIS	25.80 (2.70)
Chocolate craving	7.03 (1.72)
Chocolate liking	8.19 (1.53)
Chocolate frequency (per week)	3.08 (1.96)

Data are means (*SD*), except for gender and ethnicity, which are frequencies.

BMI, Body Mass Index; BDI, Beck Depression Inventory; TEPS, Temporal Experience of Pleasure Scale; EAT, Eating Attitudes Test; BAS, Behavioral Activation Scale; BIS, Behavioral Inhibition Scale.

Adverse effects

Table S2 reports the number of adverse effects experienced during agomelatine and during placebo. The most commonly reported adverse effects across both treatments were headache (N= 3 per treatment) and dry mouth (N= 2 per treatment). Constipation was the most commonly reported adverse effect under agomelatine that was less reported under placebo (N= 1, placebo; N=3 agomelatine).

Subjective Ratings of Stimuli

Volunteers rated the chocolate cue and taste as pleasant and the unpleasant picture and taste as unpleasant (Figure S2). Using repeated-measures ANOVA with ratings as the first factor (wanting, pleasantness and intensity), treatment as the second factor (agomelatine and placebo) and condition as the third factor (rewarding and aversion), there was no significant main effect of treatment [$F(1,16)=.954$, $p=.343$], treatment by condition interaction [$F(1,16)=1.636$, $p=.219$], rating by treatment interaction [$F(1.095,17.520)=1.172$, $p=.300$] or rating by treatment by condition interaction [$F(1.126,18.024)= .114$, $p=.770$].

Behavioural responses

To examine whether there was an effect of treatment (agomelatine/placebo) on the amount of effort invested during each condition (reward/aversion), a repeated-measures ANOVA were conducted on the number of button presses made per second during the effort phase. One participant's data was excluded due to button box failure. With treatment (agomelatine/placebo) and condition (reward/aversion) included as factors, it was revealed that there was no significant main effect of treatment [$F(1,16)=1.454$, $p=0.245$], condition [$F(1,16)=0.80$, $p=0.780$] or treatment by condition interaction [$F(1,16)=3.073$, $p=.099$] (Figure S3).

fMRI responses

Table S3 in the Supplementary Material provides a summary of the results for each contrast across all volunteers to indicate the main effect of task. Table 2 provides a summary of the results comparing agomelatine versus placebo for each phase.

Table S4 summarizes the regions in which brain activity covaried with behavioural data following agomelatine and placebo treatment for each phase. Table 3 summarizes the regions in which brain activity covaried with behavioural data comparing agomelatine versus placebo for each phase.

Table 4 summarises the results comparing agomelatine versus bupropion during each phase.

Main Effect of Task

The anticipatory phase activated brain areas, including the vmPFC and occipital regions. The effort phase activated areas such as the striatum, paracingulate gyrus and frontal cortices. The consummatory phase activated regions including the lOFC/insula (i.e. the primary taste cortex) (Rolls & McCabe, 2007) and mOFC (Table S3).

Agomelatine versus Placebo

Anticipatory Phase

Relative to placebo, agomelatine increased BOLD activity in regions such as the pgACC/vmPFC (Figure 1), dPFC and postcentral gyrus to the unpleasant cue. There were no differences in BOLD activity, between placebo and agomelatine, to the pleasant cue (Table 2).

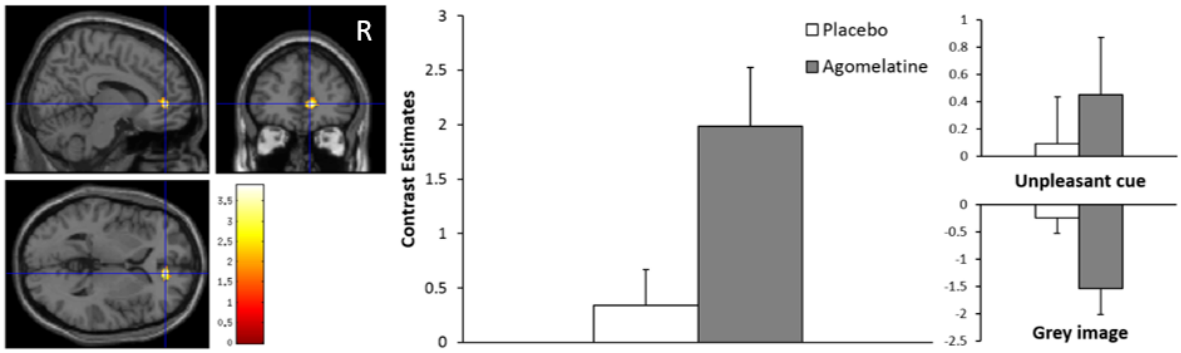

Figure 1. Unpleasant cue: *left panel*, axial, sagittal and coronal image of the pregenual anterior cingulate cortex/ventral medial prefrontal cortex (pgACC/vmPFC) activation in agomelatine versus placebo (Z= 3.24, p=0.023 family-wise error whole brain cluster corrected for multiple comparisons); *middle panel*, contrast estimates for pgACC/vmPFC centered at 10, 44, 2; *right panel,* contrast estimates for agomelatine and placebo to the unpleasant cue and grey image centered at 10, 44, 2.

Effort Phase

Relative to placebo, there was more BOLD activity after agomelatine treatment in the ACC during easy unpleasant trials compared to easy pleasant trials (Figure 2). There was also more activity after agomelatine in the insula, during hard pleasant versus easy pleasant trials. There were no differences in BOLD activity during hard unpleasant versus easy unpleasant trials or during hard unpleasant versus hard pleasant trials (Table 2).

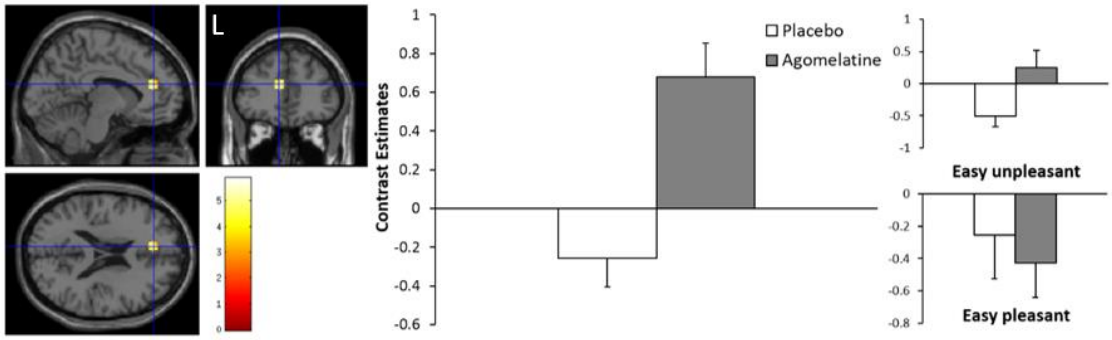

Figure 2. Easy effort unpleasant – easy effort pleasant: *left panel*, axial, sagittal and coronal image of the anterior cingulate cortex (ACC) activation in agomelatine versus placebo (Z= 4.29, p<0.001 family-wise error whole brain cluster corrected for multiple comparisons); *middle panel*, contrast estimates for ACC centered at -8, 40, 20; *right panel,* contrast estimates for agomelatine and placebo during easy unpleasant effort and easy pleasant effort centered at -8, 40, 20.

Consummatory Phase

Relative to placebo, agomelatine reduced BOLD activity to the unpleasant taste in the pre/postcentral gyrus. There were no differences in BOLD activity, between placebo and agomelatine, to the pleasant taste (Table 2).

Table 2. Regions showing significant effect of treatment on each condition.

Brain Region	MNI coordinates X	Y	Z	Z score	Significance (*p* Value)
Anticipatory[a]					
Unpleasant cue: agomelatine > placebo					
Superior frontal gyrus	-12	6	58	4.39	0.003
Postcentral gyrus	-20	-34	76	3.70	0.003
pgACC/vmPFC	10	44	2	3.24	0.023
Lingual gyrus	-4	-60	0	3.17	0.015
	4	-62	0	3.04	0.015
dPFC	20	44	30	3.10	0.023
Effort[b]					
Easy unpleasant– easy chocolate: agomelatine > placebo					
ACC	-8	40	20	4.29	<0.001
Hard chocolate – easy chocolate agomelatine > placebo					
Insula	-36	2	-16	3.95	0.042
Consummatory[b]					
Unpleasant taste: placebo > agomelatine					
Pre/postcentral gyrus	-52	-6	30	3.96	<0.001
	60	2	18	3.98	0.029

MNI, Montreal Neurological Institute; pgACC, pregenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; dPFC, dorsal prefrontal cortex; ACC, anterior cingulate cortex.

Data thresholded at [a]p=0.05 uncorrected [b]p=0.01 uncorrected

p values: Family-wise error whole brain cluster corrected

Parametric Modulation: Main Effect

During anticipation, raw wanting ratings covaried negatively with BOLD activity, in regions including the operculum cortex, after agomelatine treatment. During effort, raw wanting ratings negatively covaried with BOLD activity in the lOFC/insula following agomelatine treatment. During consummation, pleasantness ratings positively covaried with BOLD activity in the pre/postcentral gyrus following agomelatine and placebo treatment (Table S4).

Parametric modulation: Agomelatine vs Placebo

Anticipation phase

There was a stronger negative covariation between raw wanting ratings and BOLD activity in the superior parietal lobule/postcentral gyrus, after agomelatine versus placebo (Table 3).

Effort Phase

There was also a stronger positive covariation between the number of button presses made per second and BOLD activity in the midbrain/thalamus, following agomelatine versus placebo (Table 3).

Consummation Phase

There were no significant differences in the covariation between pleasantness ratings and BOLD activity during the consummatory phase (Table 3).

Table 3. Regions showing parametric modulation by subjective ratings and effort during the anticipatory, effort and consumatory phases, between agomelatine and placebo.

	MNI coordinates				
Brain Region	X	Y	Z	Z score	Significance (*p* Value)
Anticipatory[b]					
Negative relationship with raw wanting ratings: agomelatine > placebo					
Superior parietal lobule/postcentral gyrus	-40	-44	58	4.43	<0.001
Effort[a]					
Positive relationship with button presses per second: agomelatine > placebo					
Midbrain/thalamus	10	-32	-4	3.76	0.026

MNI, Montreal Neurological Institute.

Data thresholded at [a] p=0.05 uncorrected [b] p=0.01 uncorrected

p values: Family-wise error whole brain cluster corrected

No significant results for wanting ratings (absolute values) at the anticipatory phase; wanting ratings (raw and absolute values) at the effort phase; pleasantness ratings at the consummatory phase. No significant ROI results.

Agomelatine vs Bupropion

Anticipatory Phase

Relative to agomelatine, bupropion increased BOLD activity in the thalamus/hippocampus and caudate ROI to both the pleasant *and* unpleasant cue. There was also increased BOLD activity in regions such as the ACC (Figure 3), lOFC and dmPFC to the pleasant cue in the bupropion condition (Table 4).

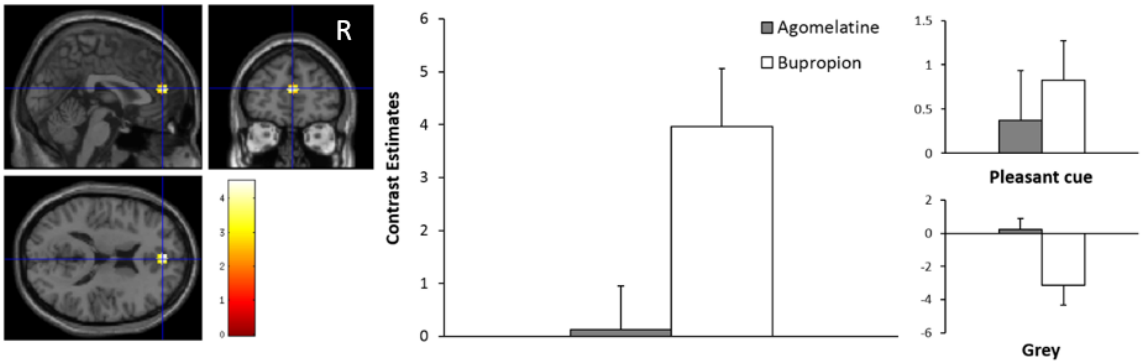

Figure 3. Pleasant cue: *left panel*, axial, sagittal and coronal image of the anterior cingulate cortex (ACC) activation in bupropion versus agomelatine (Z= 3.92, p<0.001 family-wise error whole brain cluster corrected for multiple comparisons); *middle panel*, contrast estimates for ACC centred at 2, 48, 16; *right panel,* contrast estimates for bupropion and agomelatine to the pleasant cue and grey image centred at 2, 48, 16.

Effort Phase

Relative to agomelatine, bupropion increased BOLD activity in regions such as the lOFC/insula, precuneous cortex, dmPFC, postcentral gyrus and caudate ROI during easy versus hard pleasant trials. Relative to agomelatine, bupropion increased BOLD activity during easy pleasant versus easy unpleasant trials, in regions such as the pgACC and lOFC ROI. There were no differences in BOLD activity between bupropion and agomelatine for easy unpleasant versus hard unpleasant or hard unpleasant versus hard pleasant trials (Table 4).

Consummatory Phase

Relative to agomelatine, bupropion increased BOLD activity to the unpleasant taste in the insula (Figure 4) and supramarginal gyrus. There were no differences in BOLD activity between bupropion and agomelatine to the pleasant taste (Table 4).

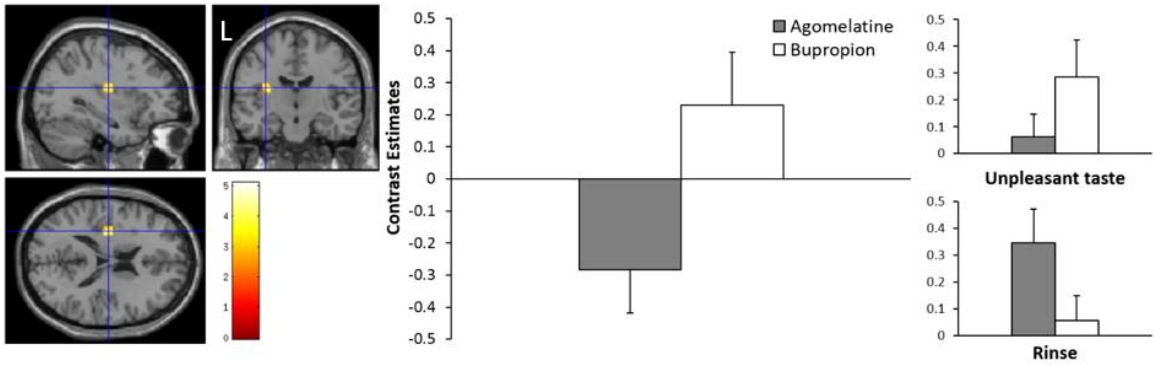

Figure 4. Unpleasant taste: *left panel*, axial, sagittal and coronal image of the insula activation in bupropion versus agomelatine (Z= 4.31, p<0.001 family-wise error whole brain cluster corrected for multiple comparisons); *middle panel*, contrast estimates for insula centred at -32, -14, 18; *right panel,* contrast estimates for bupropion and agomelatine to the unpleasant taste and rinse centred at -32, -14, 18.

Table 4. Regions showing significant effect of treatment on each condition.

	MNI coordinates				
Brain Region	X	Y	Z	Z score	Significance (*p* Value)
Anticipatory[a]					
Chocolate cue: bupropion > agomelatine					
dmPFC	-12	58	18	5.23	<0.001
Superior frontal gyrus	12	34	54	5.17	<0.001
Thalamus/hippocampus	26	-30	6	4.80	<0.001
Precentral gyrus	-56	0	30	4.47	0.002
Middle temporal gyrus	-48	-26	-12	4.23	<0.001
ACC	2	48	16	3.92	<0.001
lOFC	-28	36	-4	3.91	0.002
Caudate	10	16	4	3.99	0.015*
Unpleasant cue: bupropion > agomelatine					
Thalamus/hippocampus	24	-30	2	4.53	0.011
Caudate	10	16	4	3.66	0.043*
Effort[b]					
Easy chocolate – easy unpleasant: bupropion > agomelatine					
Middle temporal gyrus	-58	-12	-22	4.83	<0.001
Inferior frontal gyrus	-44	20	18	4.70	0.003
Superior frontal gyrus	-2	44	46	4.50	<0.001
Planum temporale	52	-2	-8	4.39	0.008
pgACC	-8	38	12	4.10	0.004
Lateral occipital cortex	50	-60	36	3.87	0.026
	-44	-62	34	3.83	0.006
lOFC	46	32	-12	4.07	0.008*
Easy chocolate – hard chocolate: bupropion > agomelatine					

lOFC/insula	42	24	-10	5.26	0.003
	-36	16	-8	4.98	<0.001
Precuneous cortex	-6	-48	56	5.06	<0.001
Paracingulate gyrus	-2	40	34	4.92	<0.001
dmPFC	0	60	20	4.11	<0.001
ACC	0	32	16	4.02	<0.001
Planum temporale	54	-2	-6	4.87	<0.001
Postcentral gyrus	-48	-34	50	3.88	0.020
	44	-24	54	3.61	0.016
Caudate	-6	10	4	4.01	0.009*
Consummatory[a]					
Unpleasant taste: bupropion > agomelatine					
Insula	-32	-14	18	4.31	<0.001
Supramarginal gyrus	-58	-26	24	3.71	0.043

MNI, Montreal Neurological Institute; dmPFC, dorsal medial prefrontal cortex; ACC, dorsal anterior cingulate cortex; lOFC, lateral orbitofrontal cortex; pgACC, pregenual anterior cingulate cortex.

Data thresholded at [a] p=0.01 uncorrected [b] p=0.001 uncorrected or *Region of Interest thresholded at p=0.05 uncorrected.

p values: Family-wise error whole brain cluster corrected or * Family-wise error corrected at the peak voxel within the ROI.

Global hemodynamic changes

A cluster centred in the lateral occipital cortex was activated across all participants to the grey image, after placebo treatment, and was thus identified as a ROI. There were no suprathreshold clusters for drug vs placebo in this region, suggesting that the observed effects of agomelatine on reward and aversion processing did not result from global hemodynamic changes.

Discussion

This study reports the effects of 7 days agomelatine treatment on neural activity during reward and aversion anticipation, effort and consummation, in healthy volunteers. Consistent with previous research, neural activity was modulated despite no alterations in motivation or subjective reports of the tastes (Dean et al., 2016; McCabe et al., 2010). We therefore suggest that acute pharmacological treatments, such as these, can initially alter neural activity without consciously modifying subjective experience. Specifically, we found that agomelatine increased neural activity during the anticipation phase for the aversive stimulus and increased activity during effort expenditure to avoid aversion, compared to obtaining reward, on easy trials. Agomelatine also decreased activity during aversion consummation. Unlike our previous results with citalopram (McCabe et al., 2010), agomelatine, did not reduce brain activity to reward or aversion. Therefore, it is possible that our results may help explain why preliminary evidence suggests that agomelatine might be more effective at improving emotional blunting, compared to SSRIs (Corruble et al., 2013).

Agomelatine increased brain activity during aversion anticipation, in regions such as the pgACC/vmPFC. This may be a mechanism of antidepressant action, as reduced activity in the pgACC/vmPFC has been found in individuals with high depression symptoms using the same task (Rzepa et al., 2017), and in depressed patients anticipating monetary loss (Ubl et al., 2015). Interestingly, research suggests that the vmPFC is involved in integrating information about the controllability of aversive outcomes, in order to regulate emotional and behavioural responses. For example, in controllable situations, activity in the vmPFC is thought to reduce the impact of aversion by reducing serotonergic release and potentially downregulating amygdala activity (Amat et al., 2005; Kerr, McLaren, Mathy, & Nitschke, 2012). Behaviourally, vmPFC activity reduces freezing and facilitates escape behaviour in rodents, reflecting more adaptive responses to aversion (Amat et al., 2005). This is particularly intriguing given that when volunteers were given control over avoiding an unpleasant taste, we found that agomelatine increased vmPFC activity, mimicking activity that you might expect in controllable situations (Amat et al., 2005; Delgado et al., 2009). Taken together future research should

examine whether agomelatine facilitates the active avoidance of aversion and whether this is related to its anxiolytic effects (Loo et al., 2002; Millan et al., 2005; Papp et al., 2006; Stein et al., 2013). Notably, bupropion also increased vmPFC/pgACC activity during the anticipation phase (Dean et al., 2016). This may suggest that catecholamine-enhancing antidepressants might be involved in preparing active responses to the environment.

Intriguingly, following agomelatine treatment, we found that during the effort phase, ACC activity increased the less a taste was wanted. Additionally, there was more activity in this region following agomelatine treatment whilst volunteers worked to avoid aversion, relative to obtaining reward, on easy trials. Given that 1) the ACC is involved in effort-based decision making, particularly in overcoming effort costs (Kurniawan, Guitart-Masip, Dayan, & Dolan, 2013; Walton, Bannerman, Alterescu, & Rushworth, 2003), and 2) agomelatine enhanced brain activity in regions such as the vmPFC/pgACC during aversion anticipation, perhaps these results suggest that agomelatine may be beneficial for assisting the active avoidance of aversion. Moreover, there was a stronger positive covariation between effort expenditure and activity in the midbrain/thalamus during the effort phase, following agomelatine, versus placebo, treatment. This is perhaps consistent with what would be expected of a dopamine-enhancing drug, given that dopamine and 5-HT_{2C} antagonists have beneficial effects on incentive-based motivation (Bailey et al., 2016; Cunningham et al., 2011; Higgins et al., 2013; Salamone & Correa, 2012; Simpson et al., 2011). Taken together, our results may suggest that agomelatine might facilitate the active avoidance of aversion. Speculatively, this might be related to preliminary evidence suggesting that agomelatine improves motivation (Gorwood et al., 2015).

During aversion consummation, agomelatine *reduced* activity in the post/precentral gyrus cortex, extending towards the primary taste cortex (Rolls & McCabe, 2007). Reduced activity in the post/precentral gyrus to the unpleasant taste is particularly interesting given that activity in this region during the consummation phase decreased with increased displeasure. This may suggest that agomelatine increased aversion processing of the

unpleasant taste, which is inconsistent with previous studies suggesting that agomelatine reduces aversion processing. For instance, in humans agomelatine reduced the startle reflex to unpleasant images (Harmer et al., 2011) and, in rodents, agomelatine reduced conditioned foot-shock vocalizations and increased the propensity to consume liquid despite being shocked (Papp et al., 2006). It would therefore be of interest for future studies to examine whether agomelatine may enhance sensory processing of aversive stimuli whilst also improving emotional regulation to aversion. If agomelatine were to facilitate the active avoidance of aversion, as our results may suggest, it is conceivable that this could help manage adversity.

Human and rodent models of depression suggest that agomelatine improves anhedonia (Di et al., 2011; El Yacoubi et al., 2011; Gargoloff et al., 2016; Martinotti et al., 2012; Papp et al., 2003). Given that reward-potentiating effects under agomelatine are apparent in stress-induced, but not control, rodents (El Yacoubi et al., 2011; Papp et al., 2003) it is possible that agomelatine may differentially affect neural activity to reward in MDD. Nonetheless, it is intriguing that agomelatine did not reduced brain activity to reward, unlike our previous results with citalopram which reduced activity to reward *and* aversion (McCabe et al., 2010). The absence of diminished brain activity to reward and aversion may explain why preliminary evidence suggests that agomelatine might be more effective than SSRIs and venlafaxine at improving anhedonia and emotional-blunting in MDD (Corruble et al., 2013; De Berardis et al., 2013; Martinotti et al., 2012). Future research is encouraged to explore this possible mechanism of action further in MDD patients.

In addition to disinhibiting dopamine and noradrenaline in the PFC via 5-HT_{2C} antagonism, agomelatine is also an agonist at MT_1 and MT_2 receptors (Stahl, 2007). MT_1 and MT_2 receptors regulate circadian rhythms via the suprachiasmatic nucleus (SCN), with the former inhibiting SCN activity and the later altering phase shifting (De Berardis et al., 2011). Given that sleep disturbance is a symptom of depression (American Psychiatric Association, 2013), it is conceivable that agomelatines melatonergic effects contribute to its ability to alleviate depression. Interestingly, whilst agomelatine is an effective antidepressant in rodents when administered either in the morning or evening,

its antidepressant effects are only attributable to its melatonergic properties when administered in the evening (Papp et al., 2003). Since agomelatine was consumed in the evening during our study, it is likely that our results were influenced by agomelatines melatonergic properties. In the context or reward and aversion processing, it is of particular interest that melatonin receptors are apparent in the dopaminergic mesolimbic system and vary according to the day-night cycle (Uz et al., 2005). Although it remains to be fully understood how melatonin interacts with the dopaminergic system, there is some evidence to suggest that melatonin can inhibit dopaminergic release (Zisapel, 2001). Moreover, given that various regions which regulate dopaminergic transmission, including the habenular, display circadian properties (Salaberry & Mendoza, 2016; Uz et al., 2005), it is likely that agomelatines melatonergic effects may influence reward and aversion processing. Consequently, how agomelatines 5-HT_{2C} antagonist and MT_1/MT_2 agonist properties interact and contribute towards reward and aversion processing requires further exploration. Future studies examining agomelatine may, therefore, benefit from investigating its effects both when administered in the morning and in the evening, in order to determine any differential effects that may be caused by the time of administration.

Comparing bupropion with agomelatine revealed that bupropion enhanced brain activity during anticipation, effort to obtain reward and consummation, as might be expected given our previous results (Dean et al., 2016). Notably, although both antidepressants increased neural activity during aversion anticipation, bupropion did so to a greater degree in the caudate and thalamus/hippocampus, whilst also potentiating activity during reward anticipation. During the effort phase, unlike agomelatine, there was more activity to easy reward trials, versus easy aversive trials, and there was more activity to easy, versus hard, reward trials, under bupropion. Whereas agomelatine reduced activity during aversion consummation, bupropion increased activity and specifically to a greater extent in the insula. Furthermore, unlike bupropion which altered both cortical and subcortical activity, agomelatine modified only cortical activity consistent with dialysis findings (Millan et al., 2003). Taken together, our results may suggest that bupropion might be more effective at altering emotional blunting, which is perhaps consistent with its broader

mechanism of action via dopamine and noradrenaline transporters, as opposed to agomelatine which primarily alters catecholamines via 5-HT_{2C} receptors.

In conclusion, we suggest a potential mechanism of antidepressant action underlying agomelatine that involves altering neural activity to aversion, whilst preserving activity to reward. Crucially, unlike SSRIs, agomelatine may improve depression symptoms without dampening positive affective symptoms. Moreover, although bupropion may be more effective at targeting reward processing, both bupropion and agomelatine might be useful for emotional blunting. This may be clinically relevant, given that blunted affect is the most frequently reported adverse psychological effect of SSRIs (Bolling & Kohlenberg, 2004). Future research is encouraged to examine these suggestions, in addition to the neural and behavioural effects of agomelatine, in MDD patients.

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Conflict of interest

Dr. McCabe has acted as a consultant to P1Vital, Givaudan, GWpharma, the British Broadcasting Company (BBC) and Channel 4. Zola Dean, Alexandra Antonesei, Dr. S. Priya Anand and Dr. Mohammed Butt report no biomedical financial interests or potential conflicts of interest.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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6. General Discussion

The overall aim of this thesis was to expand on the literature examining anhedonia in relation to Major Depressive Disorder (MDD) and its treatment. Although an abundance of evidence indicates that individuals with MDD have deficits in reward processing, it is unclear which specific aspects are impaired, as reviewed in section 1.1. Consequently, paper one aimed to examine which aspects of reward processing were impaired in individuals with high depression symptoms (HDS). More specifically, reward and aversion wanting, liking, anticipated pleasure and intensity were measured through self-report, whilst effort-expenditure was also investigated, using a novel progressive ratio task. We hypothesised that, compared to volunteers with low depression symptoms (LDS), individuals with HDS would invest less effort to obtain a pleasant taste and would report less wanting, anticipatory pleasure and intensity. We also predicted that individuals with HDS would report greater consummatory anhedonia via a questionnaire, but would not differ from volunteers with LDS in how much they liked the pleasant taste. Our results suggested, that individuals with HDS have impairments in accurately anticipating pleasure and that a subset of HDS volunteers inaccurately evaluate expended effort. They did not, however, have impairments in wanting, liking, or expending effort for, reward.

Selective serotonin reuptake inhibitors (SSRIs) have been criticized for inadequately treating anhedonia, which are the current main-line antidepressants used to treat MDD (Argyropoulos & Nutt, 2013; Boyer, Tassin, Falissart, & Troy, 2000; Dunlop & Nemeroff, 2007; McClintock et al., 2011; McMakin et al., 2012; Nierenberg et al., 1999; Nutt et al., 2007; Opbroek et al., 2002; Price, Cole, & Goodwin, 2009; Shelton & Tomarken, 2001). Instead, it has been proposed that catecholamine-enhancing antidepressants might be more effective treatments for anhedonia in MDD (Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Nutt et al., 2007; Shelton & Tomarken, 2001). However, before the completion of this thesis, it was unknown how the catecholamine-enhancing antidepressants, bupropion and agomelatine, affect reward and aversion anticipation, effort and consummation in the human brain. As a result, studies two and three sought to investigate how 7-day bupropion and 7-day agomelatine treatment impact these processes in the healthy human brain. Examining the effect of these

catecholaminergic antidepressants in the healthy human brain, prior to exploration in MDD patients, allows us to examine their mechanism of action without confounds of depression on the brain. This was achieved by utilising randomised, double-blind, placebo-controlled, crossover studies, alongside functional magnetic resonance imaging (fMRI). Given that the same task and experimental design were used to examine bupropion and agomelatine, paper three also directly compared the effects of bupropion and agomelatine on reward and aversion processing. Based on the abundance of evidence indicating that dopamine has reward potentiating effects, we hypothesised that bupropion and agomelatine would increase brain activity during reward processing, relative to placebo. As expected, bupropion increased neural activity during reward processing, however, agomelatine did not alter activity.

This general discussion begins by providing an overview of the main findings of the three studies. After discussing strengths and weakness of our research, the broader implications and recommended future directions are considered. Notably, although the main focus of this thesis is on reward processing, we also examined aversion processing in all three studies to decipher whether our findings were specific to reward processing. Our results indicate that aversion processing may be relevant in explaining our findings. Consequently, the general discussion integrates our results on reward and aversion processing, to assist with the interpretations of our findings and the broader implications.

6.1. Overview of the results

6.1.1. Paper 1: Impaired Anticipatory Pleasure in Individuals with High Symptoms of Depression during a Progressive Ratio Effort task.

As reviewed in section 2.1, anhedonia is multi-faceted and it remains unclear which specific dimensions are impaired in individuals with MDD. As a result, paper 1 aimed to examine which aspects of reward and aversion processing were impaired in individuals with HDS. More specifically, reward motivation was examined using a novel progressive ratio task, which measures how much effort (keypresses) volunteers were willing to

invest in order to receive a reward (taste of chocolate) and avoid aversion (unpleasant taste). We also examined wanting, anticipated pleasure, liking and intensity of the tastes via self-report. Task performance was examined within ninety-six healthy controls (HC), classified as having no current or previous psychiatric diagnosis. Additionally, task performance was also investigated in fifty-four volunteers who scored ≥ 17 on the Beck Depression Inventory (Beck, Steer, & Brown, 1996), and were thus classified as individuals with HDS. Performance was then compared between volunteers with HDS and a subset of fifty-three HCs, who scored ≤ 7 on the BDI, who were considered volunteers with low depression symptoms (LDS). We hypothesised that, compared to volunteers with LDS, individuals with HDS would invest less effort to obtain reward, and would report less reward wanting, anticipatory pleasure and intensity. We also predicted that individuals with HDS would report greater consummatory anhedonia via a questionnaire, but would not differ from volunteers with LDS in how much they liked the chocolate taste.

As hypothesised, we found that individuals with HDS reported greater consummatory anhedonia on the Temporal Experience of Pleasure Scale (TEPs), compared to volunteers with LDS. Interestingly, this was despite no group differences in how pleasant the chocolate taste was rated during our task. These results support previous findings, indicating that people with MDD report a reduced ability to experience pleasure via questionnaires, but report intact in-the-moment pleasure when experiencing rewarding stimuli (Berlin, Givry-Steiner, Lecrubier, & Puech, 1998; Dunn, Dalgleish, Lawrence, Cusack, & Ogilvie, 2004a, 2004b; Kaviani et al., 2004; Sherdell, Waugh, & Gotlib, 2012; Treadway, Bossaller, Shelton, & Zald, 2012; Ubl et al., 2015; Yang et al., 2014). Self-reports of consummatory anhedonia via questionnaires, but not immediately after receiving a reward, may suggest that questionnaires measuring consummatory anhedonia are actually capturing impairments in anticipating pleasure. In line with this suggestion, we found that volunteers with HDS underestimated the pleasantness of the chocolate taste (although this was a trend effect after correcting for multiple comparisons). These results suggest that individuals with HDS may not have consummatory anhedonia but may have impairments in accurately anticipating pleasure.

Unexpectedly, volunteers with HDS did not differ from those with LDS on any of the ratings, including reward wanting. Moreover, consistent with some studies, we found that individuals with HDS did not differ from volunteers with LDS in the amount of effort invested to obtain reward and avoid aversion (Cléry-Melin et al., 2011; Sherdell et al., 2012). This suggests that individuals with HDS did not want the pleasant taste less or experience impairments in overcoming the costs of effort required to obtain the reward. Consequently, our results indicate that in situations in which the cost of effort needs to be overcome, in the absence of any complex cost-benefit computations, individuals with HDS do not display signs of motivational anhedonia. Interestingly, however, we did find that a subset of volunteers with HDS underestimated how hard they worked. This suggests that there may be a subset of individuals with HDS who have impairments in accurately evaluating their performance

In addition to improving our understanding of what subcomponents of anhedonia are apparent in individuals with HDS, our results also advance our understanding of the methods used to measure motivational anhedonia. We found that, on average, volunteers continued to rate that they 1) wanted the pleasant taste and 2) wanted to avoid the unpleasant taste, even on trials when they decided to stop investing effort. Moreover, we found that, on average, volunteers predominantly invested a degree of effort to obtain reward and avoid aversion before terminating a trial, as opposed to ending a trial without investing any effort at all. This suggests that volunteers wanted to obtain the pleasant taste, and avoid the unpleasant taste, despite not investing the full amount of effort required to achieve these goals. Therefore, self-reports of reward wanting and reward-related effort expenditure may not measure the same underlying constructs. This aligns with previous evidence from the preclinical literature, reviewed in section 2.2.3, which may suggest that reward-related effort expenditure might not measure how much a reward is wanted, per se (Nunes, Randall, Podurgiel, Correa, & Salamone, 2013). Rather, it may, for instance, be a more precise measure of the ability to overcome the costs of effort (Nunes et al., 2013).

6.1.2. Paper 2: Enhanced Neural Response to Anticipation, Effort and Consummation of Reward and Aversion during Bupropion Treatment.

Paper two was the first of its kind to examine how 7-day treatment with the catecholaminergic antidepressant, bupropion, affects brain activity during reward and aversion anticipation, effort and consummation in healthy volunteers. This was achieved using a randomised, double-blind, placebo-controlled, crossover design. Seventeen healthy volunteers took bupropion for 7 days and a placebo for 7 days, separated by a two-week washout phase. After taking each drug for 7 days, volunteers underwent an fMRI scan, during which they viewed a pleasant or unpleasant cue (anticipatory phase), before keypressing (effort phase) to try and obtain the taste of chocolate or avoid an unpleasant taste (consummatory phase). Based on the literature reviewed in section 2.2 indicating a role of dopamine in reward processing, we predicted that bupropion would increase brain activity during reward anticipation, effort, and consummation.

As expected, bupropion predominately increased brain activity during reward processing compared, to placebo. More specifically, bupropion increased brain activity in the caudate, lOFC and pgACC/vmPFC to the pleasant cue. Further, there was more brain activity during high, versus low, effort after bupropion, in areas including the striatum and vmPFC. Lastly, bupropion also increased mOFC activity to the pleasant taste. These results are consistent with an abundance of studies demonstrating that dopamine-enhancing agents have reward potentiating effects, as reviewed in section 2.2.

Interestingly, bupropion also increased brain activity during aversion anticipation, effort and consummation, relative to placebo. For instance, bupropion increased activity in the vmPFC and caudate to the unpleasant cue. During the effort phase, there was more activity in the ventral striatum/caudate and primary motor cortex during easy, versus hard, effort trials. In relation to the unpleasant taste, bupropion increased activity in the mOFC, amygdala and ventral striatum. Our results demonstrate that catecholamine-enhancing antidepressants not only alter brain activity during reward processing, but also during aversion processing. This is consistent with previous findings demonstrating that

dopamine is also involved in aversion processing (Anstrom, Miczek, & Budygin, 2009; Bassareo, De Luca, & Di Chiara, 2002; Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Budygin et al., 2012; Lammel, Ion, Roeper, & Malenka, 2011; Matsumoto & Hikosaka, 2009; Navratilova, Atcherley, & Porreca, 2015; Scott, Heitzeg, Koeppe, Stohler, & Zubieta, 2006; Wenzel, Rauscher, Cheer, & Oleson, 2014).

Although bupropion altered neural activity during reward and aversion processing, effort expenditure and subjective reports of wanting, liking, and intensity were unaltered. This is also in line with previous studies examining short-term effects of medication in healthy volunteers (McCabe, Huber, Harmer, & Cowen, 2011; McCabe, Mishor, Cowen, & Harmer, 2010). This may suggest that acute bupropion treatment can increase neural activity during reward and aversion processing in healthy volunteers, without altering conscious experiences of reward and aversion.

6.1.3. Paper 3: Increased Neural Response during the Anticipation and Effort to Avoid Aversion, but not Reward, Following Agomelatine Treatment.

Paper 3 was the first to examine how 7-day treatment with the catecholamine-enhancing antidepressant, agomelatine, affects brain activity during reward and aversion anticipation, effort and consummation in healthy volunteers. This was achieved using the same experimental task and design as used in paper 2. Based on previous literature, reviewed in section 2.2, demonstrating a beneficial effect of dopamine in reward processing, we predicted that agomelatine would increase brain activity during reward anticipation, effort and consummation.

Unexpectedly, relative to placebo, agomelatine did not alter brain activity during reward anticipation, effort or consummation. This was surprising given that 1) existing evidence, in both humans and animals, suggests that agomelatine has beneficial effects on motivational and consummatory anhedonia (Bergamini, Cathomas, et al., 2016; Di Giannantonio et al., 2010; El Yacoubi, Dubois, Gabriel, Mocaër, & Vaugeois, 2011; Martinotti et al., 2012; Papp, Gruca, Boyer, & Mocaër, 2003), and 2) agomelatine is an

antagonist at serotonin $_{2C}$ receptors (5-HT_{2C}R), which has been found to have beneficial effects on reward motivation, in the preclinical literature (Bailey et al., 2016; Bezzina et al., 2015; Cunningham et al., 2011; Hayes & Greenshaw, 2011; Higgins et al., 2013; Simpson et al., 2011; Thome & Foley, 2015). Although it is worth considering that the majority of evidence in favour of agomelatine improving anhedonia are based on results from open-label, pilot trials, without placebo controls, other potential explanations for why agomelatine did not alter reward processing in healthy volunteers, are considered in 6.2.2.

Relative to placebo, agomelatine did, however, alter brain activity during aversion processing. Specifically, agomelatine increased brain activity, in regions such as the pgACC/vmPFC and dPFC, to the unpleasant cue. During effort to avoid the unpleasant taste, there was more ACC activity during easy unpleasant versus easy pleasant trials, after agomelatine treatment. Furthermore, following agomelatine treatment, there was more insula activity to hard pleasant, versus easy pleasant, trials. Finally, agomelatine decreased activity in the pre/postcentral gyrus to the unpleasant taste. A parametric modulation analysis revealed that activity in this region, during the consummatory phase, decreased with increasing displeasure ratings. Therefore, reduced activity in the pre/postcentral gyrus during aversion consummation, suggests that agomelatine increased aversion processing related to the displeasure of the taste.

Parametric modulation analyses also revealed that, relative to placebo, there was a stronger positive covariation between effort expenditure and midbrain/thalamus activity during the effort phase, after agomelatine treatment. This is perhaps consistent with what would be expected from a catecholamine-enhancing drug, given that the dopamine-rich midbrain and the thalamus are thought to be part of the reward circuitry and are involved in motivation (Haber, 2011; Haber & Knutson, 2010). Moreover, this is also in line with research indicating that 5-HT_{2C}R antagonists have beneficial effects on incentive-based motivation (Bailey et al., 2016; Cunningham et al., 2011; Higgins et al., 2013; Simpson et al., 2011).

Given that the same task and experimental design was used to examine both bupropion and agomelatine, this paper also directly compared the two antidepressants. This analysis revealed that there was more activity during the anticipatory and consummatory phases after bupropion treatment, relative to agomelatine. There were no regions that were more active during the anticipatory or consummatory phase after agomelatine treatment, relative to bupropion. More specifically, compared to agomelatine, bupropion increased activity in the caudate and thalamus/hippocampus to the unpleasant cue. Activity in the caudate and thalamus/hippocampus was also increased to the pleasant cue after bupropion treatment, in addition to the dmPFC, dACC and lOFC. During the effort phase, there was more activity in the pgACC and lOFC to easy pleasant versus easy unpleasant trials following bupropion, versus agomelatine, treatment. Moreover, there was more activity after bupropion treatment in the lOFC/insula, dmPFC, caudate and ACC, to easy pleasant versus hard pleasant trials. In relation to the consummation phase, there were no differences between bupropion and agomelatine, in brain activity to the pleasant taste. To the unpleasant taste, there was more insula activity under bupropion.

Finally, similar to our results with bupropion, agomelatine altered neural activity without affecting effort expenditure or subjective reports of wanting, liking and intensity. Although agomelatine and bupropion did not alter subjective experiences, as summarised above, they altered brain activity differently during reward and aversion processing. Given that these studies were the first of their kind to examine these drugs in relation to their neural effects during reward and aversion processing, these findings add valuable insight to the literature, as discussed below.

6.2. Consolidating the Findings across Papers

6.2.1. Integrating Paper 1 with Papers 2 and 3

One of our main findings from paper one, was that individuals with HDS underestimate how pleasant a reward will be. Although anticipated pleasure was positively related to reward-related effort-expenditure, individuals with HDS did not differ from volunteers with LDS in the amount of effort invested to obtain reward. It is possible, however, that an individual with deficits in accurately anticipating pleasure may, over time, experience

detrimental effects on reward-related effort expenditure, as discussed in further detail in section 6.4.2. Consistent with this, anticipatory anhedonia, measured via questionnaires, has been found to predict reward-related effort expenditure (Sherdell et al., 2012; Yang et al., 2014). Moreover, it has been suggested that individuals with HDS may experience motivational anhedonia, in part, due to underestimating the potential benefits of reward (Treadway et al., 2012; Treadway & Zald, 2011). It is, therefore, conceivable that underestimating pleasure could negatively imbalance a cost-benefit analysis, thereby reducing effort. Taken together, it is plausible that anticipatory anhedonia may predict later development of motivational anhedonia, although this remains to be empirically tested.

In study three, agomelatine did not alter brain activity during reward processing, in healthy volunteers. This suggests that agomelatine might not be the most suitable option for targeting reward-related symptoms. Study two, however, revealed that bupropion increased activity in the caudate and vmPFC/pgACC during the anticipatory phase, in healthy volunteers. Given that bupropion increased brain activity in these regions to both the reward and aversion cue, it is unlikely that these results suggest that bupropion increases anticipatory processes specifically related to anticipating pleasure. Rather, these effects are more likely to be related to anticipatory processes that are not valence-specific. Importantly, previous studies have demonstrated that the caudate and vmPFC/pgACC are active during anticipatory processing and are hypoactive in individuals with HDS (Bjork et al., 2004; Knutson, Fong, Adams, Varner, & Hommer, 2001; Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011; Smoski et al., 2009; Zhang, Chang, Guo, Zhang, & Wang, 2013). Therefore, the fact that bupropion increased brain activity in these regions during reward and aversion anticipation, may be a promising observation. More specifically, given that 1) our tasks involves actively obtaining reward and avoiding aversion and 2) previous evidence suggests that dopamine responds to motivationally salient stimuli, promoting reward-seeking and aversion-avoidant behaviours (Lammel et al., 2011; Matsumoto & Hikosaka, 2009; Wenzel et al., 2014), it is possible that our results could suggest that bupropion might be particularly useful for motivational processes. For instance, in relation to reward processing, bupropion might increase the saliency of reward predicting cues, which might in turn,

increase motivation to seek rewards, consistent with the incentive saliency theory of dopamine (see section 6.2.2 for a discussion in relation to aversion processing) (Berridge, 2007; Berridge & Robinson, 1998). However, this remains to be a speculation and future research should identify how bupropion alters reward anticipation and effort in individuals with HDS.

In summary, study one revealed that individuals with HDS underestimate how pleasant a reward will be. It is plausible that impairments in accurately anticipating pleasure could, over time, cause motivational anhedonia (a "loss of interest"). This is a particularly interesting, given that bupropion increased brain activity during reward and aversion anticipation and effort, in healthy volunteers. It is possible that these effects of bupropion on the neural level, may be related to increases in motivational-saliency, which could, in turn, promote reward-seeking and aversion-avoidant behaviours (see below for further discussion on aversion processing). Therefore, this may suggest a possible mechanism of action of bupropion that could be useful for MDD patients with motivational anhedonia. However, this is speculative and future examination is required.

6.2.2. Integrating Paper 2 with Paper 3

Consistent with the notion that dopamine enhances reward processing, as reviewed in section 2.2.3, we found that bupropion increased brain activity during reward anticipation, effort and consummation. Unexpectedly, agomelatine did not alter neural activity during reward processing. This suggests that not all catecholamine-enhancing antidepressants may affect reward processing. Rather, the observed effect is likely to depend on the specific pharmacological profile of each antidepressant, including the anatomical locations of where dopamine is enhanced. Bupropion increases dopamine and noradrenaline by preventing their reuptake, and has been found to increase extracellular levels of dopamine in the rat NAcc, PFC and hypothalamus (Dwoskin, Rauhut, King-Pospisil, & Bardo, 2006; Li, Perry, & Wong, 2002; Stahl et al., 2004). Agomelatine, on the other hand, increases dopamine by disinhibiting 5-HT_{2C}R, and has been found to elevate dopamine in the PFC, but not the NAcc (Millan et al., 2003; Stahl, 2007). This is

consistent with our results, as we found that bupropion altered subcortical and cortical activity, whereas agomelatine only altered cortical activity.

Notably, it was agomelatine's action as a 5-HT_{2C}R antagonist that, in part, made this catecholamine-enhancing drug particularly interesting to examine. This is since 5-HT_{2C}R agonists have debilitating effects on reward motivation, whereas 5-HT_{2C}R antagonists potentiate reward-related effort expenditure (Bailey et al., 2016; Bezzina et al., 2015; Cunningham et al., 2011; Hayes & Greenshaw, 2011; Higgins et al., 2013; Simpson et al., 2011; Thome & Foley, 2015). Additionally, it is possibly the stimulation of 5-HT_{2C}R during SSRI treatment that may potentially underlie their inability to treat anhedonia in MDD (Blier & Briley, 2011). However, 5-HT_{2C}R antagonists increase dopamine in cortical *and* subcortical regions, including the NAcc, as opposed to agomelatine which has only been found to increase dopamine in the PFC (Di Matteo, Di Giovanni, Di Mascio, & Esposito, 2000; Gobert et al., 2000; Millan et al., 2003). This suggests that additional pharmacological properties, besides its antagonistic effects at 5-HT_{2C}R, may prevent agomelatine from increasing dopamine in the NAcc. This may potentially explain why agomelatine unaltered brain activity during reward processing, as opposed to bupropion, which increased reward processing in healthy volunteers. As a result, this does not rule out the possibility that pharmacological agents which act purely as 5-HT_{2C}R antagonists, could potentiate reward processing, and should thus be examined. Additionally, it should be noted that agomelatine may affect reward processing differently in individuals with MDD than in healthy volunteers. This is possible, given that reward-potentiating effects following agomelatine treatment have been observed in stress-induced, but not control, rodents (El Yacoubi et al., 2011; Papp et al., 2003). Bupropion treatment, on the other hand, has been found to also increase reward motivation in control rodents (Bruijnzeel & Markou, 2003; Randall et al., 2015). This may also explain why bupropion, and not agomelatine, altered neural activity during reward processing in healthy volunteers. Consequently, given that evidence suggests that agomelatine improves anhedonia in MDD (Di Giannantonio et al., 2010; Martinotti et al., 2012), future research should investigate how agomelatine affects reward processing in MDD patients.

Both bupropion and agomelatine did, however, increase brain activity during aversion processing in healthy volunteers. Although we cannot ascertain whether this increased activity was specifically related to dopamine functioning, this is consistent with evidence indicating that dopamine is involved in aversion processing (Anstrom et al., 2009; Bassareo et al., 2002; Bromberg-Martin et al., 2010; Budygin et al., 2012; Lammel et al., 2011; Matsumoto & Hikosaka, 2009; Navratilova et al., 2015; Scott et al., 2006; Wenzel et al., 2014)More specifically, given that bupropion and agomelatine increased brain activity during aversion anticipation and effort to avoid aversion, our results may be in line with the theory that dopamine modulates the active avoidance of aversion (Bergamini, Sigrist, et al., 2016; Gentry, Lee, & Roesch, 2016; Oleson, Gentry, Chioma, & Cheer, 2012; Wenzel et al., 2014; Winter et al., 2007). Speculatively, dopamine may affect aversion processing through a similar mechanism as it is suggested to affect reward, in the incentive salience theory of dopamine, in which dopamine is thought to make a reward desired by giving it a positive and alerting value (Berridge, 2007; Berridge & Robinson, 1998). It is plausible that this theory may also extend to aversion, in which the saliency of aversive stimuli is enhanced, thereby increasing motivation to avoid it i.e. dopamine regulates motivational salience (Bassareo et al., 2002; Bromberg-Martin et al., 2010; Lammel et al., 2011). Another possibility, is that both agomelatine and bupropion, might regulate emotional responses during anticipation, to facilitate active responses to the environment (e.g. actively avoid aversion). This is consistent with evidence suggesting that vmPFC activity may be involved in regulating emotional responses when aversion can be avoided (Amat et al., 2005; Delgado, Jou, LeDoux, & Phelps, 2009; Kerr, McLaren, Mathy, & Nitschke, 2012).

If dopamine can facilitate aversion-avoidant behaviours, this could be a potential mechanism underlying the antidepressant effect of catecholamine-enhancing antidepressants. For example, it has been suggested that there may be different subgroups of MDD patients who respond differently to aversion, with some patients being hypersensitive to aversion (negative potentiation theory) and others having blunted responses to aversion (emotional context incentive theory) (Rottenberg, Gross, & Gotlib,

2005). If the speculated mechanism of action of catecholamine-enhancing antidepressants was supported, it may suggest that catecholaminergic antidepressants might be useful for both subtypes. More specifically, enhancing the motivational salience of aversion may be particularly beneficial for patients experiencing damped negative and positive affect (i.e. emotional blunting). Equally, if catecholamines can improve the ability to proactively respond to, and avoid, aversion, they could conceivably prevent negative interactions with the environment and, over time, alleviate negative affect. Therefore, catecholaminergic antidepressants could also be beneficial for MDD patients who are hypersensitive to aversion. However, given that dopaminergic antidepressants and the role of dopamine in aversion processing are both understudied, this speculation requires empirical examination.

6.3. Strengths and Limitations of the Studies

All three studies included in this thesis measured multiple dimensions of reward processing within the same task, which is often not attempted or inappropriately tested. For instance, the majority of previous studies use secondary rewards (e.g. money) which may not adequately measure reward consummation. This is since it is the *anticipation* of spending money that gives it a rewarding value. Our studies, on the other hand, use primary (taste) rewards, which allows anticipatory, effort and consummatory phases to be dissociated. Beneficially, in paper one, this allowed the observation that volunteers with HDS did not have deficits in some aspects of reward processing (e.g. wanting or liking), but did have impairments in other dimensions (e.g. accurately anticipating pleasure). Moreover, we demonstrated that volunteers may want an outcome yet not invest enough effort to obtain it, indicating that subjective ratings of wanting and effort expenditure are not necessarily measuring the same construct. In studies two and three, our paradigm enabled us to identify which brain areas were affected by catecholamine-enhancing antidepressants during anticipatory, effort and consummatory phases. Whilst we believe that we adequately separated wanting from liking, as stated in section 2.1, it is difficult to obtain a pure measure of any single dimension. As an example, the consummatory phase of neuroimaging studies does not exclusively measure reward 'liking'. Rather, it is likely to also capture saliency processing, which is difficult to isolate from pleasure. As a result, it is unclear whether alterations in neural activity during any

one phase (e.g. consummation) is related to any one specific psychological process (e.g. liking).

The interpretation of neuroimaging results is often deduced through reverse inference, based on previous findings, which can be flawed (Poldrack, 2011). In an attempt to improve the inferences of our results, paper three included additional analyses, in which brain data was covaried with subjective ratings on a trial-by-trial basis. Although parametric modulation analyses help identify relationships between brain activity and behaviour, this technique is not without limitations. For instance, it relies on the assumption that the visual analogue scales, used to measure subjective experiences, are sensitive enough to capture minute variations and that participants report their experiences accurately. To further assist with the interpretations of our results, we additionally examined both reward *and* aversion processing, which helped identify whether our findings were specific to one valence. The importance of including both conditions is particularly emphasized in paper two, in which we found that bupropion similarly altered brain activity during reward and aversion processing in overlapping areas. Whilst this was a strength of our studies, as mentioned in section 2.2.2, preclinical evidence demonstrates that pleasure and displeasure is processed within incredibly localised regions (Castro & Berridge, 2014). More specifically, the neural substrates of pleasure and displeasure can be a cubic-millimetre in size, and within close proximity of one another, which would be spatially indistinguishable using fMRI (Castro & Berridge, 2014; Smith & Berridge, 2007). Therefore, although our experiments improve on studies that do not include the abovementioned methods, limitations still remain.

Although there are strengths to measuring reward-related effort expenditure via button pressing, such as the similarities to methods used in the preclinical literature (Thomsen, 2015), there are some disadvantages. For instance, there may be more sensitive and ecologically valid techniques, such as measuring force-grip or physical exercise (Cléry-Melin et al., 2011). Unfortunately, we observed a ceiling effect in keypressing performance across all three studies. More specifically, in relation to paper one, our task may not have been difficult enough to detect group differences in aversion-related effort

expenditure. However, given that we did find within-group differences between reward and aversion conditions, this suggests that our task adequately measured reward-related effort expenditure. Nevertheless, the task in paper one would be improved by increasing the progressive ratio schedule, thus making it more difficult. With regards to studies two and three, the effort phase was bounded by time, in order to ensure that there were some trials where volunteers would be successful at obtaining reward and unsuccessful at avoiding aversion. Whilst this was necessary to ensure that volunteers received the pleasant and unpleasant taste, there is a practical limit on how much effort can be physically exerted in six seconds. Given that we examined healthy volunteers, it can be theorised that participants performed at optimum level under placebo. Therefore, any potential benefits of catecholamine-enhancing drugs on effort expenditure would likely be undetected. Consequently, although we can conclude that the catecholaminergic antidepressants used in studies two and three did not reduce effort expenditure, we cannot determine whether effort expenditure may have been improved. For instance, if an additional behavioural task had been included, in which effort was measured over a longer period of time without time constraints, this may have yielded more variable data, which may have been more sensitive to detect changes in effort expenditure.

Disadvantages, specific to paper one, include that we did not exclusively recruit volunteers with either subthreshold MDD or clinical MDD. Instead, we recruited volunteers experiencing HDS, regardless of whether they had a MDD diagnosis or not. Although we recorded the number of volunteers with a MDD diagnosis, which is not commonly done in studies using a similar recruitment method (Franzen & Brinkmann, 2016; Yang et al., 2014), we cannot ascertain whether or not those without a diagnosis would have met criteria for MDD if they had been clinically assessed. Ideally, a psychiatrist should have performed an assessment during the screening session, to determine whether volunteers with HDS met subthreshold or clinical MDD. Preferably, a HC, subthreshold MDD and a clinical MDD group would have been examined, in order to determine which aspects of anhedonia are present in individuals at risk of MDD, versus those with clinical depression. Therefore, although our findings are highly relevant to MDD, we cannot ascertain whether our results indicate potential predisposing factors for MDD or clinical characteristics. Nevertheless, identifying that individuals with HDS

have impairments in accurately anticipating pleasure and evaluating high effort performance indicates potential targets for preventative and/or treatment strategies.

Another advantage of our studies is that we had very strict exclusion criteria for our HC samples, thereby ensuring high quality HC groups. This did, however, have detrimental effects on recruitment, particularly for the pharmacological fMRI studies, as we had to exclude a large proportion of people during screening. Indisputably, a high-quality HC group is essential for a well-controlled experiment, and is thus a priority. However, pharmacological fMRI experiments, in particular, might be better suited to projects with fewer time and resource restrictions, to allow for the recruitment of large samples. The low sample sizes in papers two and three are problematic, as they lead to a lack of statistical power. Parallel to this, in our fMRI studies, we occasionally used a lenient cluster-defining threshold of p=0.05, which is above the recommended cluster-defining threshold of p=0.001 (Eklund, Nichols, & Knutsson, 2016). As a result, it is important to consider that there may be an inflation in the number of false positives in our fMRI results. The paper by Eklund and colleagues, which identifies the pitfalls of making clusterwise inferences based on fMRI analyses that use parametric tests with lenient thresholds, was published a month after paper two was published. Although we could have reported the data from paper three using a more conservative threshold, we kept this consistent with paper two to allow direct comparisons of the results, given that the experimental designs were the same. Although our results should be interpreted with caution, it is noteworthy that our results were generally consistent with the pharmacological profiles of each antidepressant and the regions were similar to those commonly reported in the reward and aversion literature. Given that these studies were the first to examine the effects of these antidepressants on reward anticipation, effort and consummation in the human brain, our studies offer preliminary results which we hope will encourage future large-scale experiments. In the future it is advised that non-parametric permutation tests are considered for analysing fMRI data, as they do not make assumptions which are often violated by parametric tests (Eklund et al., 2016).

In paper two, we examined activity in five regions of interest (ROI) by applying a small volume correction (SVC) without correcting for multiple comparisons. Notably, our result of increased pgACC/vmPFC activity to the pleasant cue following bupropion treatment would not have survived a Bonferroni correction for the number of SVCs performed. This should, therefore, be taken into consideration when interpreting the results. Following advice from a reviewer on a manuscript later submitted by our lab, we combined the ROIs into a single mask when performing ROI analyses in paper three. Whilst this alteration may be considered a more conservative approach than was used in paper two, a more stable and recommended approach is to perform group level comparisons on the average signal intensity extracted from ROIs (Poldrack, 2007). Consequently, this approach will be considered in the future.

An advantage specifically related to studies two and three, is that we utilised randomised, double-blind, placebo-controlled, crossover studies, which are considered the gold standard of pharmacological trials. Disadvantages, however, include that we cannot ascertain whether all volunteers took the medications. It would have been beneficial to have obtained, for instance, plasma samples to measure the presence of bupropion and agomelatine, to ensure treatment compliance (Patil et al., 2012; Zhu et al., 2012). Another disadvantage is that we cannot determine whether the observed effects of bupropion and agomelatine on brain activity were specific to the dopamine-enhancing properties of each antidepressant. The addition of positron emission tomography (PET) scanning would have been one method of establishing whether the observed treatment-induced changes in brain activity were related to dopamine function in regions such as the striatum (Schott et al., 2008). Finally, although our results indicate the neural targets of bupropion and agomelatine during reward and aversion processing in healthy volunteers, our results cannot be generalised to MDD patients. Consequently, replication is required in individuals with a diagnosis of MDD.

6.4. Broader Implications and Future Directions

6.4.1. Researching Anhedonia in Major Depressive Disorder

In order to improve our understanding of reward-related symptoms in MDD, it is fundamental that future research adopts the terms which subdivide anhedonia, rather than use 'anhedonia' to refer to reward deficits more broadly. Further, it is essential that terms are used consistently across studies, so that clear interpretations of results can be made, allowing for research to progress quickly and efficiently. Related to this, it is important that future studies carefully consider the methods used to examine specific reward-related constructs. For example, as identified in paper one, reward liking may not be adequately measured using questionnaires that require an individual to imagine how pleasurable an event would be. Additionally, although reward-related effort expenditure is commonly used in the preclinical literature to measure reward wanting, it may actually be a more precise measure of the ability to compute cost-benefit analyses (Nunes et al., 2013; Treadway & Zald, 2011). Therefore, research should focus on improving current, and developing new, techniques to better isolate different aspects that may contribute to cost-benefit computations. Moreover, we emphasise the importance of measuring more than just one aspect of reward processing within a single task. This will allow for more accurate interpretations of results, which will improve our understanding of what dimensions of reward processing are impaired in MDD, which will, in turn, guide treatment.

6.4.2. Consummatory Anhedonia in Major Depressive Disorder

As reviewed in section 2.1.1, although the loss of pleasure is a core symptom of MDD, our results and the majority of previous findings, suggest that individuals with HDS do not experience consummatory anhedonia. However, it is important to consider that some MDD patients may experience consummatory anhedonia and could go undetected in some experiments due to limitations regarding inclusion criteria. More specifically, studies examining anhedonia in MDD often recruit volunteers regardless of whether or not they are experiencing symptoms of anhedonia. Given the substantial heterogeneity of MDD, and considering that not all patients experience anhedonia (Van Loo, De Jonge, Romeijn, Kessler, & Schoevers, 2012), it is possible that consummatory anhedonia may

be observed if recruitment was limited to patients experiencing, clinically defined, anhedonia. Equally, it is possible that consummatory anhedonia could develop after severe, or prolonged, deficits in other reward-related domains (as discussed further below). These possibilities require investigation, as they could account for why there are contradictory findings within the literature, since some studies do observe reduced pleasure in MDD (Dunn et al., 2004a, 2004b; Kaviani et al., 2004). However, it is difficult to recruit individuals experiencing severe symptoms of anhedonia, likely because they are less motivated to participate in research. As a result, it would be beneficial for institutions with access to patients experiencing severe symptoms of anhedonia, to examine for the presence of consummatory anhedonia.

Following on from the above, it is possible that consummatory anhedonia could proceed impairments in other reward-related aspects, such as the inability to accurately anticipate pleasure. For instance, although we did not find reduced in-the-moment pleasure responses, we did find that individuals with HDS underestimate how pleasant a reward will be and a subset of HDS volunteers underestimate how hard they have worked (perceived effort). It is conceivable that impairments in both anticipatory pleasure and perceived effort could, over time, reduce motivation to engage in positive activities, as is characteristic in MDD. Consistent with this, anticipatory pleasure has been found to predict reward-related effort expenditure (Sherdell et al., 2012; Yang et al., 2014). It is plausible that withdrawal from engaging in pleasurable activities, may over time cause them to be less enjoyed when experienced (e.g. disengaging from a hobby may negatively impact performance, causing the activity to be less pleasurable). It would, therefore, be of interest for longitudinal studies to examine whether impairments in, for instance, anticipating pleasure, could over time lead to motivational anhedonia, which could then potentially induce consummatory anhedonia.

6.4.3. Motivational Anhedonia in Major Depressive Disorder

Motivational anhedonia is a complex symptom and there are various factors that could contribute towards a “loss of interest”. In light of our results and previous findings, reviewed in section 2.1.2, it is possible that individuals with HDS do not have deficits in

reward wanting or in overcoming the costs of effort to obtain rewards, when simple cost-benefit analyses are required. It is possible, however, that individuals with HDS have difficulties in overcoming other costs, such as the possibility of not being rewarded despite achieving a goal. Additionally, they may underestimate the benefits of rewards, as suggested by a reduced ability to accurately anticipate pleasure and self-evaluate performance, which may suggest a blunted sense of achievement. This suggestion is in line with previous studies, indicating that individuals with HDS choose to invest less effort when the reward is large and the probability of being rewarded is uncertain (Yang et al., 2014). Therefore, although our study demonstrates that individuals with HDS do not have impairments in overcoming the costs of effort, it remains to be examined what specific costs may be overestimated, and what benefits are underestimated.

Reduced motivation could also be explained by more general impairments in higher-level cognitive functioning. For example, executive functions, such as working memory, are known to be impaired in individuals with HDS (Snyder, 2013). Consequently, individuals with HDS may have impairments in integrating vast amounts of information to determine whether the perceived benefits of the reward outweigh the costs associated with it. This is conceivable given that we, and others (Sherdell et al., 2012), have not found group differences in reward-related effort expenditure when the task is simple and thus the cost-benefit analysis is easier to compute. By contrast, studies using the EEfRT have reported that individuals with HDS are less willing to expend effort for rewards, compared to HCs (Treadway et al., 2012; Yang et al., 2014). Given that the EEfRT varies numerous aspects, including reward magnitude and reward probability, whereas our task only manipulates effort, this suggests that group differences may only be apparent when cost-benefit analyses are harder to compute. Due to the complexity of the EEfRT, it is unclear if motivation is impaired because of the overestimation of specific costs (reward probability) and underestimation of specific benefits (reward magnitude), or possibly because of a more general deficit in computing complicated cost-benefit analyses.

To examine this further, a future study could use a simple task that requires little information processing, and gradually alter what information needs to be computed.

Importantly, the effect of additional factors (e.g. probability) on reward-related effort expenditure should be examined in isolation and then in combination with other factors (e.g. magnitude). This will help establish whether impairments are specifically related to, for instance, reward magnitude, or the cognitive load of having to compute multiple aspects at once. Measures of executive function, particularly working memory, should also be included to help determine whether any impairments are the result of more general higher-level cognitive deficits.

If future research reveals that motivational anhedonia is related to impairments in computing cost-benefit analyses, it is conceivable that these impairments could extend further to contexts involving aversion. Consequently, studies examining reward-related motivation should also examine motivation to avoid aversion. This will help disentangle whether any observed impairments are specific to the processing of reward-related information. Interestingly, the emotional context insensitivity theory of MDD suggests that some patients experience reduced positive and negative affective reactivity (emotional blunting) (Rottenberg et al., 2005). It is intriguing to consider whether the clinical criterion 'anhedonia' is actually capturing emotional blunting, as opposed to a construct specific to reward. For instance, it is possible that someone who reports a loss of interest in engaging in pleasurable events, such as hobbies, may also experience reduced motivation to escape displeasure, such as leave a job where they are unhappy. However, this is only a thought for consideration and would require empirical investigation.

6.4.4. Prevention and Treatment of Anhedonia in Major Depressive Disorder

Psychological

Cognitive Behavioural Therapy (CBT) is the recommended first-line form of psychotherapy for MDD (Health, 2017). Behavioural Activation (BA) is a component of CBT, which aims to alleviate MDD by encouraging patients to engage in more positive, and less negative, activities (Hopko, Lejuez, Ruggiero, & Eifert, 2003). During BA,

patients record their daily activities and their emotional responses to them, including achievement, closeness and enjoyment (Hopko et al., 2003; Vivyan, 2014). Collaboratively, therapists work with patients to monitor and evaluate which activities elicit the most positive and negative emotional responses, which are then scheduled more or less frequently, accordingly (Hopko et al., 2003). Based on our findings and others (Sherdell et al., 2012; Yang et al., 2014), it might be therapeutically beneficial to not only record experienced pleasure, but to additionally evaluate anticipated pleasure to a given event. This is because we demonstrated that individuals with HDS underestimate how pleasant a reward will be, and assisting MDD patients to identify this deficit may encourage them to persist engaging in pleasurable activities, or to reengage if they have already withdrawn. Crucially, it is possible that individuals with HDS may also have impairments in retrospectively recalling pleasure, in addition to prospectively imagining pleasure. Consequently, it is important that patients are able to report experienced pleasure during an activity. This highlights the potential utility of using mobile applications (apps) to support treatment, which is an emerging area of research (Ly, Carlbring, & Andersson, 2012).

Another component of CBT is cognitive restructuring, whereby maladaptive thoughts are challenged and updated with more adaptive cognitions (Clark & Beck, 2010). In addition to helping MDD patients revise any negative biases regarding the likelihood of experiencing pleasure, it may also be beneficial to target perceptions in relation to performance. For instance, we found that a subset of individuals with HDS underestimated how hard they worked. It is plausible that negatively evaluating high-effort performance may suggest that some individuals with HDS experience less positive feedback, such as achievement, from expending effort. Speculatively, over time this could cause withdrawal from being actively engaged with activities that may typically elicit pleasure, such as hobbies. Consequently, future research is encouraged to explore whether underestimating performance can lead to later developments of motivational anhedonia and whether this can be prevented using cognitive interventions.

Pharmacological

At present, SSRIs are the recommended first-line pharmacological treatments for MDD, regardless of a patients presenting symptoms (Grundmann, Kacirova, & Urinovska, 2015; Health, 2017). This is, perhaps, astonishing, considering that there are 227 possible combinations of symptoms that can result in a MDD diagnosis (Van Loo et al., 2012). Therefore, there is enormous potential for symptoms to vary between individuals with the same MDD diagnosis. Consequently, it may be a therapeutic benefit to work towards a more personalised treatment approach, in which patients are treated depending on their specific symptoms, as opposed to diagnosis alone (Insel, 2009). Indeed, it is conceivable that using a more tailored treatment approach could improve remission rates of MDD, which currently is only achieved by approximately ¼-½ of SSRI-treated patients (Nierenberg et al., 2010; Nutt et al., 2007).

It has been proposed that SSRIs may potentially be effective at treating symptoms such as low mood and anxiety, but not for the loss of pleasure and interest, which may be better targeted by catecholaminergic antidepressants (Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Nutt et al., 2007; Shelton & Tomarken, 2001). Our results suggest that, perhaps, not all catecholamine-enhancing antidepressants affect reward anticipation, effort and consummation, in the healthy human brain. Rather, it is likely to depend on the specific pharmacological profile of each antidepressant, including the anatomical locations of where dopamine is enhanced. In light of our results, and others reviewed in section 2.3.2, it is possible that bupropion might be an especially useful antidepressant for targeting reward-related symptoms in MDD, particularly motivational anhedonia. Moreover, given that bupropion increased pgACC/vmPFC and mOFC activity during reward processing in healthy volunteers, whereas the SSSRI, citalopram, reduced activity in the ventral striatum and vmPFC/mOFC (McCabe et al., 2010), this may support the notion that catecholaminergic antidepressants could be more suitable treatments for anhedonia in MDD. Although there is some preclinical evidence to suggest that bupropion improves, whereas SSRIS exacerbate, motivational deficits (Yohn et al., 2015), there are no trials in humans that have directly compared the efficacy of bupropion versus SSRIs at improving anhedonia in MDD. This is, therefore, a crucial area to investigate.

Although we did not observe any effects of agomelatine on neural activity during reward processing in healthy volunteers, it is important to consider that there is evidence to suggest that agomelatine improves anhedonia in MDD (Di Giannantonio et al., 2010; Martinotti et al., 2012). Indeed, as discussed in section 6.2.2, a number of reasons could explain why agomelatine did not affect reward processing in healthy volunteers, and thus further research is warranted in MDD. Given that the SSRI, citalopram, reduced neural activity to reward (McCabe et al., 2010), whereas agomelatine did not, it is intriguing to consider that agomelatine could, by comparison, be more useful than SSRIs at treating anhedonia in MDD. For example, it is possible that switching from an SSRI to agomelatine could result in improved reports of anhedonia, simply by alleviating SSRI-induced inhibitions on reward activity. From the two trials demonstrating that agomelatine improves self-reports of anhedonia in MDD, it is unclear if the participants in these trials were previously medicated and terminated SSRI treatment prior to taking part in the study (Di Giannantonio et al., 2010; Martinotti et al., 2012). If so, it is possible that anhedonia improved because SSRI treatment was terminated and subsequent agomelatine use did not blunt neural activity to reward. Unfortunately, comparisons were made to baseline measures as opposed to a placebo control and may, thus, be worth investigating. Moreover, it is conceivable that agomelatine might be useful in combination with SSRIs, as it could potentially prevent the debilitating effects of SSRIs on reward processing by antagonising 5-HT_{2C}R. However, these speculations remain to be examined.

In addition to attenuating brain activity during reward processing, the SSRI, citalopram, also reduced neural activity during aversion processing in healthy volunteers (McCabe et al., 2010). In contrast, we are the first to show that both bupropion and agomelatine increases brain activity during aversion processing in healthy subjects. These opposing effects of catecholaminergic versus serotonergic antidepressants on aversion processing, may suggest that the former class of antidepressants might be more effective treatments for emotional blunting. Consistent with this, there is some preliminary evidence to suggest that bupropion and agomelatine might be less associated with affective blunting

compared to SSRIs. For instance, one study found that compared to 58% of SSRI-treated patients, only 21% of agomelatine-treated patients reported a lack of 'emotional intensity' (Corruble, de Bodinat, Belaïdi, & Goodwin, 2013). Similarly, fewer patients report emotional blunting during bupropion, versus SSRI, treatment (Goodwin, Price, De Bodinat, & Laredo, 2017). However, both of these studies did not statistically compare agomelatine or bupropion with SSRIs and thus further investigation is required. Moreover, in addition to being an emotional deficit, emotional blunting could also be a motivational impairment, including a global loss of energy and interest (Demyttenaere & Jaspers, 2008). As outlined in section 6.4.3, it is possible that patients presenting with a loss of interest to engage in pleasurable activities, may also have a flattened interest to engage in other, less pleasurable but necessary activities, such as chores or going to work. Consequently, future studies that investigate the potential benefits of catecholamine antidepressants on reward motivation, should additionally examine their effects on motivation, interest and energy more broadly, rather than being just limited to reward.

Following on from the above, it is essential that research investigates the role of catecholamines in aversion processing. Although dopamine is predominately discussed in relation to reward, the results from ourselves and others indicate that catecholamines are also involved in aversion processing (Anstrom et al., 2009; Bassareo et al., 2002; Bergamini, Sigrist, et al., 2016; Bromberg-Martin et al., 2010; Budygin et al., 2012; Lammel et al., 2011; Matsumoto & Hikosaka, 2009; Oleson et al., 2012; Scott et al., 2006; Wenzel et al., 2014). Unfortunately, research examining the role of catecholamines in aversion processing is substantially underdeveloped, compared its research on reward processing. Rather than being reward-specific, it is possible that catecholamines might be, more generally, involved in promoting active responses to the environment (i.e. actively seeking rewards and avoiding aversion) (Anstrom et al., 2009; Bassareo et al., 2002; Matsumoto & Hikosaka, 2009; Wenzel et al., 2014). Consistent with this, in addition to promoting reward-seeking behaviours, there is some evidence from the preclinical literature suggesting that dopamine may be involved in the active avoidance of aversion (Bergamini, Sigrist, et al., 2016; Bromberg-Martin et al., 2010; Gentry et al., 2016; Matsumoto & Hikosaka, 2009; Oleson et al., 2012; Winter et al., 2007). However, this remains to be extensively examined, especially in humans. Our findings of increased

brain activity during aversion anticipation and effort to avoid aversion following both bupropion and agomelatine treatment, may provide support to this theory and should thus be examined further. Establishing whether catecholaminergic antidepressants could improve the ability to actively respond to aversion, could suggest a potential beneficial mechanism of antidepressant action underlying catecholaminergic antidepressants. As discussed in section 6.2.2, if catecholamines can improve the ability to proactively respond to, and avoid, aversion, they could conceivably prevent negative interactions with the environment and, over time, alleviate negative affect. However, it is equally possible that enhanced aversion processing during catecholaminergic treatment in healthy volunteers, could suggest a negative pharmacological profile for anxious MDD patients. Consequently, an improved understanding of the role of dopamine in aversion processing, especially in relation to facilitating the active avoidance of aversion, and its subsequent effects on mood, is crucial.

6.5. Conclusions

The body of work included in this thesis expands the literature examining anhedonia in relation to MDD and its treatment. We examined which aspects of reward processing are impaired in individuals with HDS, using a novel progressive ratio task and explicit measures of wanting, anticipated pleasure, liking and intensity. Consistent with previous literature, our results demonstrate that the ability to experience pleasure immediately after receiving a reward is not impaired in individuals with HDS (Arrondo et al., 2015; Berlin et al., 1998; Clepce, Gossler, Reich, Kornhuber, & Thuerauf, 2010; Dichter, Smoski, Kampov-Polevoy, Gallop, & Garbutt, 2010; Dichter, Tomarken, Shelton, & Sutton, 2004; Forbes, Miller, Cohn, Fox, & Kovacs, 2005; Sherdell et al., 2012; Swiecicki et al., 2009). This is in spite of individuals with HDS reporting consummatory anhedonia via questionnaires (Berlin et al., 1998; Sherdell et al., 2012; Treadway et al., 2012; Ubl et al., 2015; Yang et al., 2014). Rather, our findings suggest that individuals with HDS have a diminished ability to accurately anticipate pleasure. This may explain why individuals with HDS report experiencing consummatory anhedonia via questionnaires, which may rely on reward anticipation, but not immediately after receiving a reward. Moreover, our results demonstrate that individuals with HDS do not have impairments in reward-related effort expenditure, when solely the amount of effort required to obtain the reward is

manipulated. This suggests that individuals with HDS do not have impairments in overcoming the costs of effort, when simple cost-benefit analyses are required. It is possible, however, that individuals with HDS overestimate other costs associated with seeking rewards, and/or underestimate the potential benefits of receiving rewards (Treadway et al., 2012; Treadway & Zald, 2011). For instance, in addition to underestimating how pleasant a reward would be, we also found that a subset of individuals with HDS underestimated how hard they worked. Therefore, underestimating the amount of pleasure, and potentially a reduced feeling of achievement, may be some of the factors that could cause the perceived benefits of rewards to be underestimated. Our results could also suggest that motivational anhedonia is only apparent in individuals with HDS when complicated, and not simple, cost-benefit analyses are required. In addition to potentially identifying useful preventative and/or treatment targets for individuals with HDS, our results also have important implications regarding the methods used to measure consummatory and motivational anhedonia. For example, as demonstrated in the preclinical literature, we highlighted that reward-related effort expenditure does not necessarily signify reward wanting, rather it may instead measure the ability to overcome the cost of effort or compute cost-benefit analyses (Nunes et al., 2013).

We also examined how two catecholamine-enhancing antidepressants, bupropion and agomelatine, affect reward and aversion processing in the healthy human brain. We found that bupropion increased, whereas agomelatine did not alter, brain activity during reward processing. These results indicate that not all catecholamine-enhancing antidepressants affect neural reward anticipation, effort and consummation. Rather, it is likely to depend on the specific pharmacological profile of each antidepressant, including the anatomical locations of where catecholamines are enhanced. Importantly, our results indicate that bupropion and agomelatine do not dampen brain activity during reward processing in healthy volunteers, unlike SSRIs (McCabe et al., 2010). This may offer some support to the notion that catecholaminergic antidepressants could be more suitable treatments than SSRIs at treating anhedonia in MDD (Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Nutt et al., 2007; Shelton & Tomarken, 2001). Interestingly, we also demonstrated that catecholaminergic antidepressants increase brain activity during the anticipation,

effort to avoid, and consummation of aversion. Taken together with the existing literature, our findings suggest that catecholaminergic antidepressants may be useful for targeting emotional blunting.

In light of our results and the previous literature, future research should attempt to dissociate which specific aspects contribute to motivational anhedonia. For instance, studies should examine potential costs that may be overestimated, and benefits which may be underestimated, in effort-based decision making. It should also be established whether impairments in computing cost-benefit analyses, in relation to obtaining rewards and avoiding aversion, are related to higher-level cognitive dysfunction. In relation to improving the treatment of anhedonia in MDD, future studies should continue to unravel the specific relationship between different neurotransmitters and the many subdivisions of reward and aversion processing. For example, a particular area that remains understudied is the role of dopamine in actively avoiding aversion. With continued investigation into what specific symptoms are presented in MDD, and their underlying neurobiological mechanisms, it is conceivable that more personalised and effective treatments could be developed, improving MDD remission rates (Insel, 2009).

6.6. References

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7. Supplementary Material and Appendices

7.1. Supplementary Material: Paper 1

Impaired Anticipatory Pleasure in Individuals with High Symptoms of Depression during a Progressive Ratio Effort task.

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S1. Rest duration

After each trial, all volunteers had a rest time of at least that seen under 'rest duration' (Table S1). Due to satiety effects, it was desirable to have volunteers prompted with each trial at roughly as close in time as possible. To achieve this, we varied the rest duration so that people who quit waited slightly longer than those who did not. At the same time, we did not want the rest time to be substantially long in case it could be interpreted as a punishment. To reduce the likelihood of this happening, we increased the rest duration for quitters, but not enormously or consistently (we also envision that since the rest duration allowed volunteers to relax their hand, this too would reduce the likelihood of this time being viewed as a punishment). The average amount of time it takes to complete a trial (average time taken: ATT) was determined via piloting. If a trial terminated (either by completing the required keypresses or by pressing 'q') after the ATT, then the rest duration was that seen under 'rest duration' in Table S1. If a trial was completed by pressing the required number of keypresses before the ATT, then the rest duration was the 'rest duration' plus the time difference between the ATT and completion time. If a trial was terminated by pressing 'q', the rest duration was that seen under 'quit rest duration' in Table S1.

Table S1. The resting duration for each trial depending on if volunteers quit or not.

Trial	Rest Duration (milliseconds)	Quit Rest Duration (milliseconds)
1	2000	4000
2	4000	5000
3	6000	8000
4	8000	10000
5	10000	13000
6	11000	15000
7	12000	16000
8	13000	18000
9	14000	19000
10	15000	20000
11	15000	21000
12	15000	22000

S2. Correlations with reward, and aversion, -related effort expenditure

Given that we aim to examine reward, and aversion, -related effort expenditure, we conducted non-parametric partial correlations controlling for pre-task levels of general motivation.

Reward-related effort expenditure

HC

Keypresses to obtain reward did not correlate with scores on the BAS drive or trait TEPs consummatory subscale. Keypresses to obtain reward did correlate with the TEPS anticipatory subscale but did not survive correction for multiple comparisons. Keypresses to obtain reward also correlated with how much volunteers wanted, expected to like, liked and the intensity of, the pleasant taste (although pleasantness did not survive correction for multiple comparisons) (Table S2a).

HDS

Keypresses to obtain reward did not correlate with scores on the BAS drive, trait TEPs anticipatory or consummatory subscale. Keypresses to obtain reward did correlate with how much volunteers wanted, expected to like, liked and the intensity of the pleasant taste (although intensity did not survive correction for multiple comparisons) (Table S2a).

Table S2s. Correlations between keypresses to obtain reward and reward-related measures, controlling for pre-task levels of motivation, in healthy controls and volunteers with high symptoms of depression.

			BAS drive	TEPS A	TEPS C	Wanting	Exp. Pleas.	Pleas.	Intensity
KP	HC	r_s	-0.018	-0.214	0.160	0.468	0.405	0.272	0.329
		p	0.861	0.045 (0.318[a])	0.127	<0.001	<0.001	0.008 (0.059[a])	0.001
	HDS	r_s	-0.039	0.064	-0.173	0.664	0.615	0.429	0.370
		p	0.793	0.663	0.224	<0.001	<.001	0.002	0.007 (0.052[a])

KP, keypresses; HC, healthy controls; HDS, high symptoms of depression; BAS drive, Behavioural Activation Scale drive subscale; TEPS A, Temporal Experience of Pleasure Scale anticipatory subscale; TEPS C, Temporal Experience of Pleasure Scale consummatory Subscale; Exp. Pleas., expected pleasantness; Pleas., pleasantness.

[a] Did not survive correction for multiple comparisons

Aversion-related effort expenditure

HC

Keypresses to avoid aversion correlated with how much volunteers wanted to avoid the unpleasant taste, prior to correction for multiple comparisons. Keypresses to avoid aversion did not correlate with how much volunteers expected to dislike or disliked the unpleasant taste, nor with how intense it was (Table S2b).

HDS

Similar to HC volunteers, keypresses to avoid aversion correlated with how much HDS volunteers wanted to avoid the unpleasant taste, although this effect did not survive correction for multiple comparisons. Further, keypresses to avoid aversion did not correlate with how much they expected to dislike the unpleasant taste, nor with how intense it was. Unlike HC, how much volunteers with HDS disliked the unpleasant taste

did correlate with keypresses to avoid aversion, although this effect did not survive correction for multiple comparisons (Table S2b).

Table S2b. Correlations between keypresses to avoid aversion and subjective reports of the unpleasant taste, controlling for pre-task levels of motivation, in healthy controls and volunteers with high symptoms of depression.

			Wanting	Expected pleasantness	Pleasantness	Intensity
KP	HC	r_s	0.215	0.162	0.052	0.164
		p	0.041 (0.164 [a])	0.124	0.634	0.126
	HDS	r_s	0.318	0.241	0.321	0.146
		p	0.024 (0.096 [a])	0.091	0.023 (0.092 [a])	0.313

KP, keypresses; HC, healthy controls; HDS, high depression symptoms.

[a] Did not survive correction for multiple comparisons

S3. Data analysis

Pre/post response speed was calculated as the number of keypresses made per second (kp/s), averaged over three 15 second trials. Due to experimental error, 1 HC and 1 HDS volunteer did not have data for response speed. Since pre/post-task response speed was measured to control for potential differences in motor ability and fatigue, only data from volunteers with useable data from the effort phase were included in the analysis of response speed.

Where possible, missing questionnaire items were interpolated using the average item response on that questionnaire or, where appropriate, subscale. Since attention may have been compromised when completing the post-session questionnaires, data from questionnaires that included reverse items were excluded if the reversed items were not consistent with non-reversed item responses (classified as above/below 2 standard deviations from their average response. Where the standard deviation was zero, a response above/below 1 Likert scale was used).

Two volunteers with HDS did not complete the post-session trait questionnaires. 1 volunteer with HDS had missing BMI data, 1 volunteer with LDS did not complete the mood VAS, 1 LDS volunteer had missing data for agitation, 1 HDS and 1 HC had missing chocolate frequency data and 3 HDS and 3 HC had missing MCI data.

Volunteers who reported disliking the pleasant taste (1 HDS) or liking the unpleasant taste (2 HC; 1 HDS), were excluded from analyses involving stimuli of that valence. Due to experimental error, 4 HCs (3 LDS) had missing pleasantness and intensity ratings for the unpleasant taste. To allow for direct comparisons between the pleasant and unpleasant taste, the ratings for the unpleasant taste were converted to the same scale as the pleasant taste, by subtracting each value from 100 i.e. the higher the score the more negative the experience (excluding aversive intensity which was already on the same scale as the pleasant taste). Due to missing data primarily from the aversion condition, where possible, statistical tests were performed separately for reward and aversion conditions to retain as much data as possible for each rating.

Data from 3 volunteers (1 HC, 2 HDS) were excluded from analyses involving the experimental task as they asked whilst completing the task if they could press ‘q’,

suggesting that they did not fully understand the task instructions (HC: n=95; LDS: n=53; HDS: n=53). Due to time constraints, 1 volunteer with HDS only had data for the reward block. One LDS volunteer made no keypresses on the reward block and thus their data was removed from the analysis of kp/s.

S4. Demographic details of volunteers with high symptoms of depression

Table S4. Depression, psychotropic medication and psychotherapy status of volunteers with high symptoms of depression

Depression diagnosis	
Diagnosed with depression	9/54 (16.67%)
Length of diagnosis	<1 year (n=1) 1-2 years (n=3) 3-4 years (n=2) 5-6 years (n=2) 10 years (n=1)
Psychotropic medication status	
Current	5/54 (9.26%) Citalopram (n=2) 10mg/day for 1m (prev. higher dose for 2yrs) 40mg/day for 6m Sertraline (n=2) 50mg/day for 3m (prev. higher dose for 9month) 100 mg/day for 3years Melatonin (n=1) Only when sleep disturbed
Previous	4/54 (7.41%) Fluoxetine (n=1) 8m, 4years ago Mirtazapine (n=1) 3m, 18m ago Melatonin (n=1) 1 year ago, one-off use Clozapine (n=1) 2years, 8years ago Unknown antidepressants 2m, 1yr ago
Psychotherapy status	
Current	6/54 (11.11%) Counselling (n=5) CBT & integrative therapy (n=1)
Previous	16/54 (29.63%) Counselling (n=12) CBT (n=1) Talking therapies (n=1) Unknown (n=2)

S5. Group differences on questionnaires that did not measure mood or anhedonia

Given that volunteers with LDS and HDS significantly differed on questionnaires that do not measure depression or anhedonia, each variable was correlated with the number of keypresses performed on the task to determine whether they affected task performance. Depending on the questionnaire, correlations were preformed either with the total number of keypresses (Table S5a) or keypresses made on the reward (Table S5b) or aversion (Table S5c) block only. Since higher scores on the EAT questionnaire are related to greater concerns about calorific food, this measure was correlated with the total number of keypresses made to obtain the more calorific drinks (i.e. the pleasant *and* the unpleasant taste). The only significant result was that within HDS volunteers, the more frequently they consumed chocolate the more keypresses they made on the reward block (although, this did not survive correction for multiple comparisons p=.063). Given that A) the groups did not differ on chocolate liking B) chocolate craving did not correlate with performance on the reward block, and C) groups did not differ on any of the subjective ratings of the chocolate taste used in this task, we believe it is unlikely that frequency alone would substantially affect performance on the task and was thus not included as a covariate in the main analyses.

Table S5a. Correlations between overall keypresses and questionnaire responses that significantly differed between volunteers with low and high symptoms of depression.

			Age	**BMI**	**BIS-11**	**STAI**	**MCQ**	**EAT**
KP	LDS	r_s	-0.101	-0.201	-0.185	-0.158	0.041	-0.171
		p	0.472	0.150	0.185	0.259	0.770	0.231
	HDS	r_s	-0.047	-0.107	0.050	-0.081	-0.117	-0.087
		p	0.746	0.460	0.731	0.575	0.427	0.557

KP, keypresses; LDS, low depression symptoms; HDS, high depression symptoms; BMI, Body Mass Index; EAT, Eating Attitudes Test; STAI, State Trait Anxiety Inventory; MCQ, Monetary Choice Questionnaire.

Table S5b. Correlations between keypresses to obtain reward and questionnaire responses that significantly differed between volunteers with low and high symptoms of depression.

			Choc Craving	Choc frequency
KP	LDS	r_s	-0.150	-0.112
		p	0.282	0.425
	HDS	r_s	0.080	0.373
		p	0.571	0.007

KP, keypresses; LDS, low depression symptoms; HDS, high depression symptoms

Table S5c. Correlations between keypresses to avoid aversion and questionnaire responses that significantly differed between volunteers with low and high symptoms of depression.

			BIS
KP	LDS	r_s	0.069
		p	0.644
	HDS	r_s	0.055
		p	0.720

KP, keypresses; LDs, low depression symptoms; HDS, high depression symptoms; BIS, Behavioural Inhibition Scale

S6. Pre-task state measures

Table S6. Pre-task state measures for volunteers with low and high symptoms of depression.

	HC	LDS	HDS	*U*	Sig[a]	*r*
Motivation	5.81 (2.37)	5.82 (2.30)	4.84 (2.50)	901.500	0.001	-0.31
Sadness	0.54 (1.11)	0.54 (1.10)	2.69 (3.92)	612.50	<0.001	-0.49
Happiness	7.50 (2.15)	7.23 (2.67)	5.11 (1.96)	599.00	<0.001	-0.49
Anxiety	0.97 (1.88)	1.02 (1.92)	2.63 (3.99)	862.00	0.001	-0.33
Agitation	0.52 (1.08)	0.43 (1.10)	1.29 (2.02)	918.00	0.003	-0.029
Hunger	4.22 (2.69)	4.24 (2.74)	2.96 (2.66)	950.500	0.004[b]	-0.28

Data are median (interquartile range)

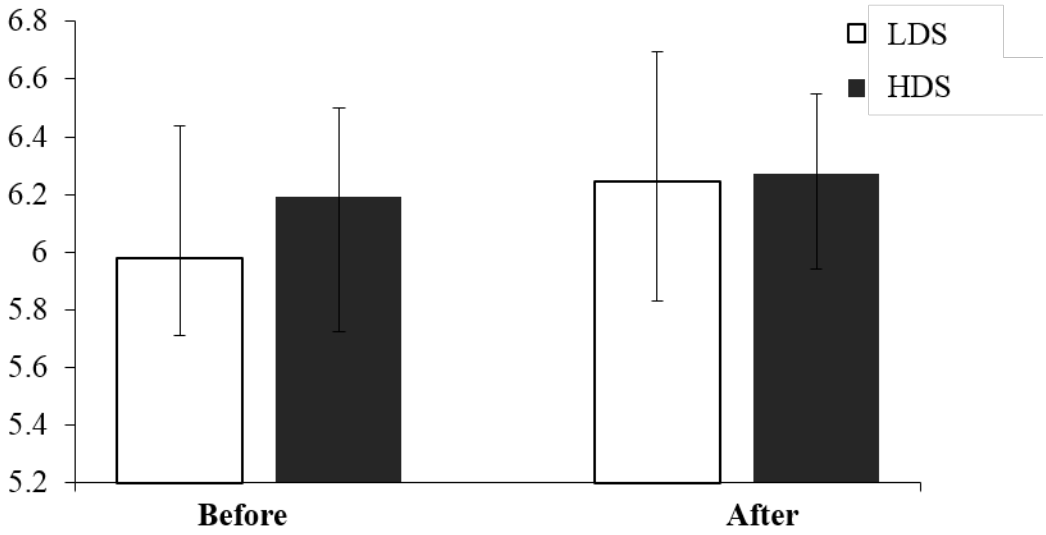
HC, healthy controls; LDS, low depression symptoms; HDS, high depression symptoms

[a]Comparisons between volunteers with LDS and HDS

[b]Given that hunger was unlikely to be related to depression, a correlation was performed to determine whether hunger was related to task performance. This was not significant in either volunteers with LDS (r_s =-0.049, p=0.728) or HDS (r_s =0.054, p=0.711).

S7. Response speed

Figure S7. Pre/post task response speed between volunteers with low and high symptoms of depression. Bar plots represent the medians and error bars show the interquartile range (IQR).



S8. Aversion Intensity

Intuitively, the more un/pleasant a taste is, the more intense it is likely to be. However, for the unpleasant taste, a proportion of data did not follow this trend (HC: n=26; LDS: n=12; HDS: n=6), with volunteers disliking the unpleasant taste i.e. above 50/100, but rating it as not very intense i.e. below 50/100 (e.g. some volunteers rated the unpleasant taste as the maximum possible for unpleasantness i.e. 100/100, but the minimum possible for intensity i.e. 0/100, which is incredibly unlikely). It is quite likely that these volunteers *did* find the taste intense but, due to the negative valence, used the intensity scale incorrectly. As a result, and for completeness of the data, we converted the intensity values for anyone who rated the unpleasant taste with a value bellow 50 (suggesting dislikingly) and rated intensity below 50 (suggesting not intense), by subtracting the intensity value from 100 (i.e. in the above example, where someone rated the unpleasant taste as 100/100 unpleasant and 0/100 intense, their intensity rating was converted to 100-0 = 100).

HC

Volunteers did not differ in their ratings of how intense the pleasant taste (Mdn= 75.45, IQR=15.21) versus the unpleasant taste was (Mdn=73.00, IQR=17.00) (Z=-1.322, p=0.186).

HDS

Unlike HC, volunteers with HDS considered the pleasant taste (Mdn=81.00, IQR=19.57) to be more intense than the unpleasant taste (Mdn=73.00, IQR=19.17) (Z=-2.081, p=0.037).

LDS vs HDS

Volunteers with LDS and HDS did not differ in how intense they considered the unpleasant taste (U=1279.00, p=0.525).

S9. Quitting behaviour

HC

39.78% of volunteers completed the maximum number of keypresses on both blocks. More volunteers (72.04%) completed the maximum number of keypresses on the aversion block compared to the reward block (46.32%).

51/95 (53.68%) volunteers quit on the reward block, compared to 26/93 (27.96%) volunteers on the aversion block. After the first quit, 86.67% of volunteers performed keypresses on the remaining reward trials and completed, on average, 22.54% (IQR=40.25) of the remaining keypresses. After the first quit, 100% of volunteers performed keypresses on the remaining aversion trials and completed, on average, 51.75% (IQR=73.11) of the remaining keypresses.

HDS

40% of volunteers completed the maximum number of keypresses on both blocks. Similar to HC, more HDS volunteers (70.59%) completed the maximum number of keypresses on the aversion block compared to the reward block (44.23%).

29/52 (55.77%) volunteers quit on the reward block compared to 15/51 volunteers (29.41%) on the aversion block. After the first quit, 100% of volunteers made keypresses on the remaining reward trials and completed, on average, 36.79% (IQR=43.23) of the remaining keypresses. After the first quit, 91.67% of volunteers performed keypresses on the remaining aversion trials and completed, on average, 76.56% (IQR=61.42) of the remaining keypresses.

Table S9a. The number of times volunteers quit on each block (out of a possible 12, separated into quartiles). We found that both HC and DS volunteers made more quits on the reward block than the aversion block. The table shows that, of those who quit at least once, the biggest difference was that more volunteers quit between 4-6 times on the reward block than the aversion block

		0 quits	1-3 quits	4-6 quits	7-9 quits	10-12 quits	Sum
Reward	**HC**	44	26	18	4	3	95
		46.32%	27.3%	18.95%	4.21%	3.16%	100%
	LDS	27	13	10	1	2	53
		50.94%	24.53%	18.87%	1.89%	3.77%	100%
	HDS	23	15	12	2	0	52
		44.23%	28.85%	23.08%	3.85%	0%	100%
Aversion	**HC**	67	21	4	1	0	93
		72.04%	22.58%	4.30%	1.08%	0%	100%
	LDS	40	11	2	0	0	53
		75.47%	20.75%	3.77%	0%	0%	100%
	HDS	36	13	2	0	0	51
		70.59%	25.49%	3.92%	0.00%	0.00%	100%

HC, healthy control; LDS, low depression symptoms; HDS, high depression symptoms.

Table S9b. The earliest trial number when volunteers quit (out of a possible 12, separated into quartiles. We found that both HC and DS volunteers quit earlier on the reward block than the aversion block. The table shows that, of those who quit at least once, the biggest difference was that more volunteers made their first quit during trials 7-9 on the reward block compared to the aversion block.

		Trials 1-3	**Trials 4-6**	**Trials 7-9**	**Trials 10-12**	**Never quit**	**Sum**
Reward	**HC**	4	8	21	18	44	95
		4.21%	8.42%	22.11%	18.95%	46.32%	100%
	LDS	2	5	10	9	27	53
		3.77%	9.43%	18.87%	16.98%	50.94%	100%
	HDS	1	6	14	6	25	52
		1.92%	11.54%	26.92%	11.54%	48.08%	100%
Aversion	**HC**	2	4	8	12	67	93
		2.15%	4.30%	8.60%	12.90%	72.04%	100%
	LDS	2	1	2	8	40	53
		3.77%	1.89%	3.77%	15.09%	75.47%	100%
	HDS	1	0	7	7	36	51
		1.96%	0.00%	13.73%	13.73%	70.59%	100%

HC, healthy control; LDS, low depression symptoms; HDS, high depression symptoms.

7.2. Supplementary Material: Paper 2

Enhanced Neural Response to Anticipation, Effort and Consummation of Reward and Aversion during Bupropion Treatment.

Running title:

Effect of Bupropion on Neural Reward.

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Figure S1. Visual depiction of a reward-hard trial- all ISI and ITI are jittered.

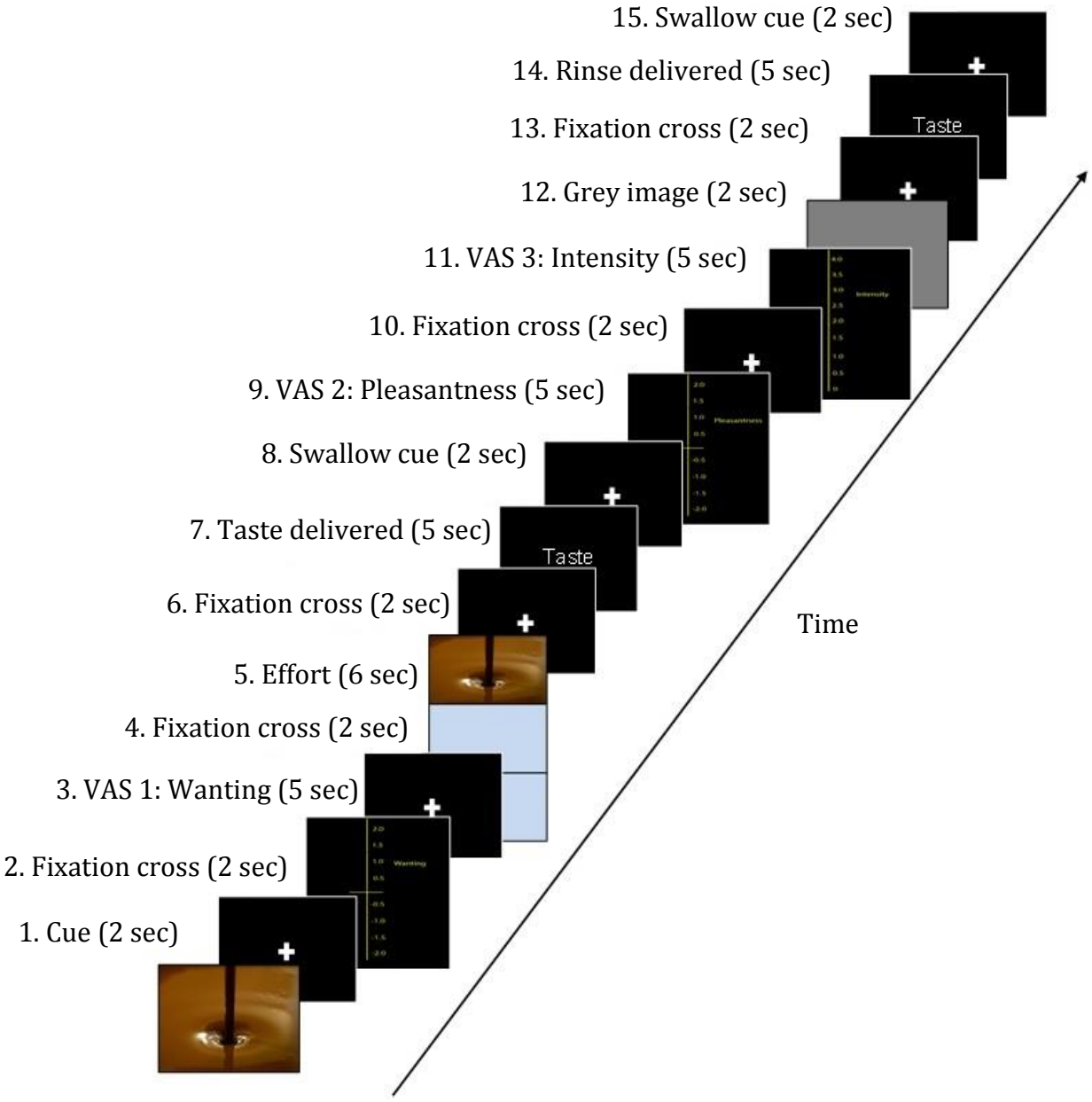


Table S1. Regions showing main effect of task irrespective of treatment for all subjects.

	MNI coordinates				
Brain Region	X	Y	Z	Z score	Significance (*p* Value)
Anticipatory					
Chocolate cue – grey image					
Occipital Lobe	-18	-94	8	6.46	<0.001
Superior Frontal Gyrus	-10	34	60	6.25	<0.001
dmPFC	26	54	32	6.01	<0.001
Angular gyrus	-46	-56	46	5.92	<0.001
	46	-50	44	5.44	<0.001
Lateral occipital cortex	30	-86	8	5.71	<0.001
Mid Cing	0	-16	40	5.20	<0.001
Temporal occipital fusiform cortex	40	-48	-22	4.88	0.002
Pre/postcentral gyrus	-62	-6	28	4.70	<0.001
Midbrain	2	-32	-14	4.60	0.003
Postcentral gyrus	-38	-20	40	4.54	0.020
Cerebellum	-12	-46	-22	4.51	0.039
lOFC	42	26	-6	4.48	0.020
Thalamus/hippocampus	-16	-36	4	4.48	0.010
Unpleasant cue – grey image					
Occipital lobe	-16	-92	6	7.00	<0.001

	18	-88	-2	6.63	<0.001
dlPFC	30	52	32	6.05	<0.001
Angular gyrus	46	-50	44	5.94	<0.001
dmPFC	-22	50	38	5.63	<0.001
Temporal occipital fusiform cortex	-38	-50	-28	5.31	<0.001
	42	-48	-26	4.83	<0.001
Superior Frontal Gyrus	-12	34	60	5.12	<0.001
Hippocampus/thalamus	20	-30	-6	4.41	0.003
Mid Cing	0	-16	40	5.08	<0.001
Middle Temporal gyrus	54	-58	0	4.82	0.007
Supramarginal gyrus	-54	-46	36	4.82	<0.001
Planum temporale	-54	-30	8	4.79	<0.001
Frontal Pole	12	38	58	4.76	0.002
pgACC	4	54	4	4.72	<0.001
Pre/postcentral gyrus	-56	-6	26	4.58	0.004
lOFC	-42	46	-4	4.57	0.039
Putamen	-28	-24	0	4.46	0.001
Lateral occipital cortex	36	-76	28	4.24	0.029
	Effort				
Hard chocolate – easy chocolate					
Precentral gyrus	-34	-24	56	6.27	<0.001
Insula	32	20	6	4.83	0.001

Supramarginal gyrus	60	-36	18	4.27	0.010
Parietal Operculum cortex	-44	-28	22	4.59	<0.001
Mid Cing	0	-12	56	3.99	<0.001
Putamen	-30	-12	0	3.69	<0.001
lOFC	50	22	-4	4.39	0.002*
Easy chocolate – hard chocolate					
Cuneal cortex	12	-84	24	4.76	0.003
Easy unpleasant – hard unpleasant					
Cuneal cortex/occipital pole	10	-86	18	4.48	0.001
Hard unpleasant – easy unpleasant					
Post/precentral gyrus	-46	-22	58	5.94	<0.001
	36	-18	48	3.70	0.004
Occipital lobe	-24	-92	0	5.81	0.006
Operculum cortex	46	16	2	3.68	0.033
lOFC	30	28	-12	3.68	0.033
Consummatory					
Chocolate taste - rinse					
Ventral striatum	6	4	-6	3.33	0.010*
Insula	-30	16	2	2.86	0.018
OFC/Frontal pole	26	44	-8	4.29	0.018
Caudate	-14	14	14	3.34	0.010*
Unpleasant taste - rinse					

Amygdala	-18	-6	-20	3.88	0.011
Insula	-36	10	-14	3.47	0.011
lOFC	-32	36	-12	3.56	0.011

MNI, Montreal Neurological Institute; lOFC, lateral orbitofrontal cortex; Cing, cingulate; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; Mid Cing, middle cingulate; ACC, anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; dmPFC, dorsal medial prefrontal cortex.

Data thresholded at $p \leq 0.05$

p values: Family-wise error whole brain fully corrected or *family-wise error small volume correction $p<0.05$.

Figure S2.

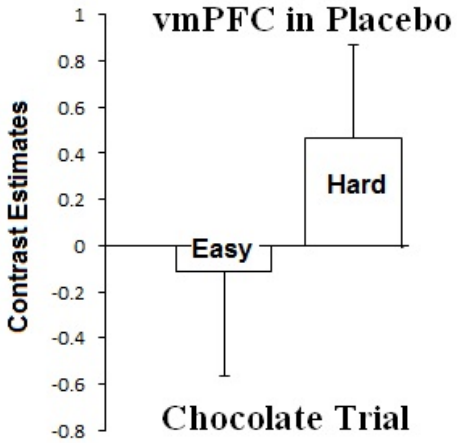

vmPFC in Placebo
Contrast Estimates
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
Hard
Easy
Chocolate Trial

Table S2. Subjective state ratings pre- and post-scan after 7 days of treatment with bupropion and placebo, separated by a two-week washout phase. There were no significant effects of treatment condition on any of the measures.

Measure	Bupropion Mean (SD)		Placebo Mean (SD)	
	Pre-scan	Post-scan	Pre-scan	Post-scan
VAS				
Alertness	5.35(2.05)	3.67 (2.66)	6.18 (2.38)	5.85 (7.56)
Disgust	1.39 (1.27)	1.79 (1.86)	0.92 (1.22)	1.69 (1.71)
Drowsiness *	2.96 (2.49)	3.89 (2.83)	1.73 (1.56)	4.03 (2.53)
Anxiety *	2.05 (2.03)	0.90 (0.74)	1.34 (1.38)	0.80 (0.89)
Happiness *	6.18 (1.61)	5.00 (2.68)	6.65 (1.76)	5.68 (2.29)
Nausea	0.61 (0.76)	1.29 (2.20)	0.65 (0.90)	1.28 (2.05)
Sadness	0.91 (0.78)	0.92 (1.35)	0.67 (0.52)	0.98 (1.90)
Withdrawn	0.93 (0.92)	1.55 (1.79)	1.15 (1.26)	1.15 (0.99)
Faint *	0.54 (0.66)	1.58 (1.95)	0.87 (1.25)	1.61 (1.95)
Total BFS score *	18.20 (11.03)	21.20 (12.63)	12.33 (9.80)	19.33 (12.51)

SD, standard deviation; VAS, visual analogue scale (n=17); BFS, the Befindlichkeit Scale (n=15); Repeated measure analyses of variance; p>0.05; *Significant main effect of time (pre/post scan) p<0.05.

Table S3. Frequencies of Adverse Effects Reported Under Bupropion (*n*=17) and Placebo (*n*=17).

Adverse Event	Placebo	Bupropion
Gastrointestinal symptoms		
Diarrhoea	2	1
Constipation	1	0
Dry Mouth	0	2
Nausea or vomiting	1	1
Heart symptoms		
Palpitations	0	1
Dizziness when standing	1	1
Chest pain	0	1
Skin symptoms		
Rash	1	1
Increase perspiration	0	0
Itching	1	0
Dry skin	2	1
Nervous system symptoms		
Headache	5	5
Tremors	0	0
Poor coordination	0	1
Dizziness	0	4

Eye and ear symptoms		
Blurred vision	1	0
Ringing in the ears	0	0
Genital and urinary symptoms		
Difficulty urinating	1	0
Painful urination	0	1
Frequent urination	0	1
Menstrual irregularity	0	0
Sleep symptoms		
Difficulty sleeping	3	3
Sleeping too much	3	0
Sexual functioning		
Loss of sexual desire	0	1
Trouble achieving orgasm	0	0
Trouble with erections	0	0
Other symptoms		
Anxiety	0	2
Fatigue	3	5
Poor concentration	1	1
Decreased energy	1	3
General malaise	0	1
Restlessness	0	1

Other		
Decreased appetite	0	1
Increase Energy	0	1
Irritable	0	1

Data are frequencies.

Figure S3. Subjective pleasantness, wanting and intensity ratings of the pleasant and unpleasant stimuli in placebo and bupropion conditions. There were no significant effects of treatment condition on any of the measures.

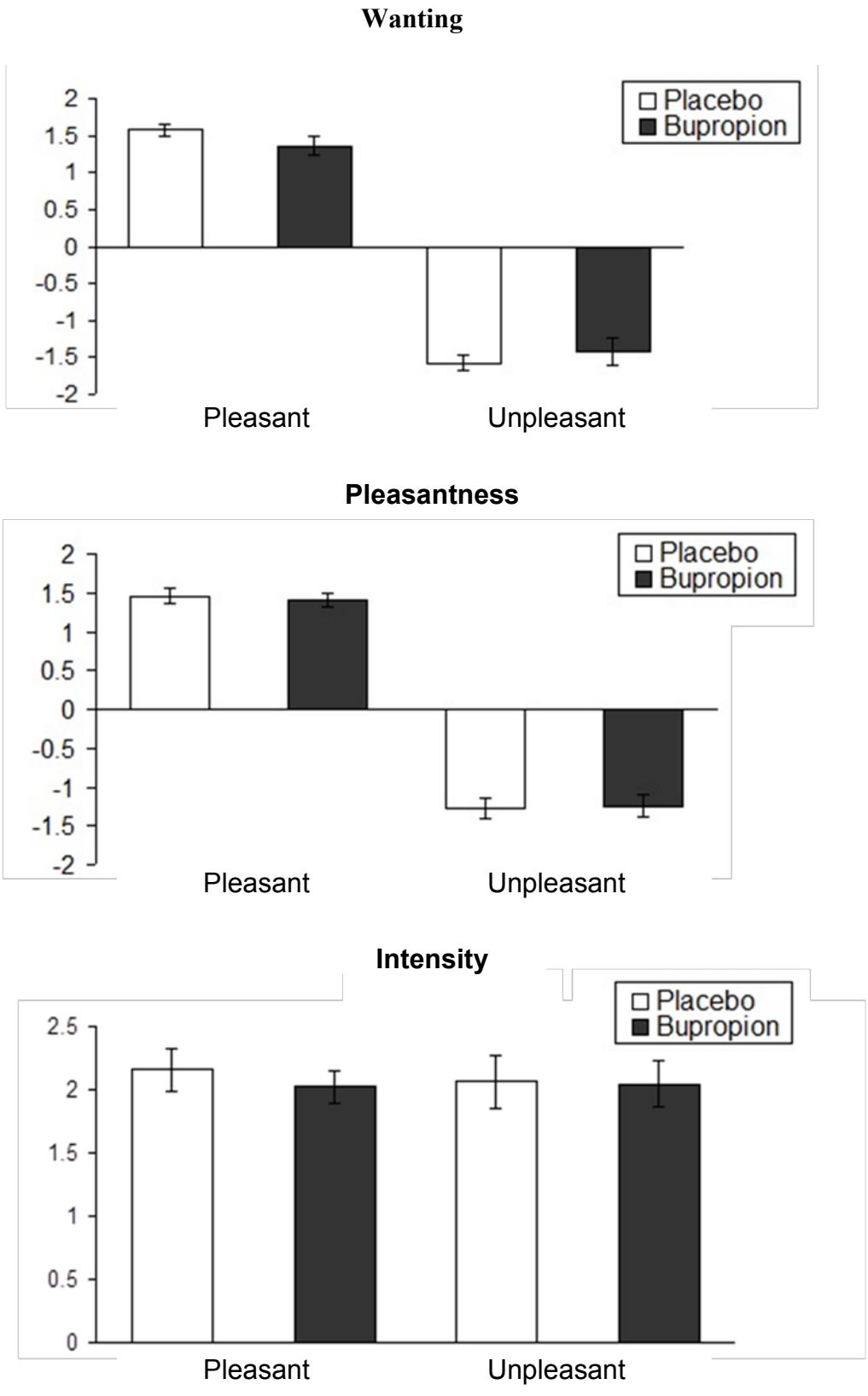
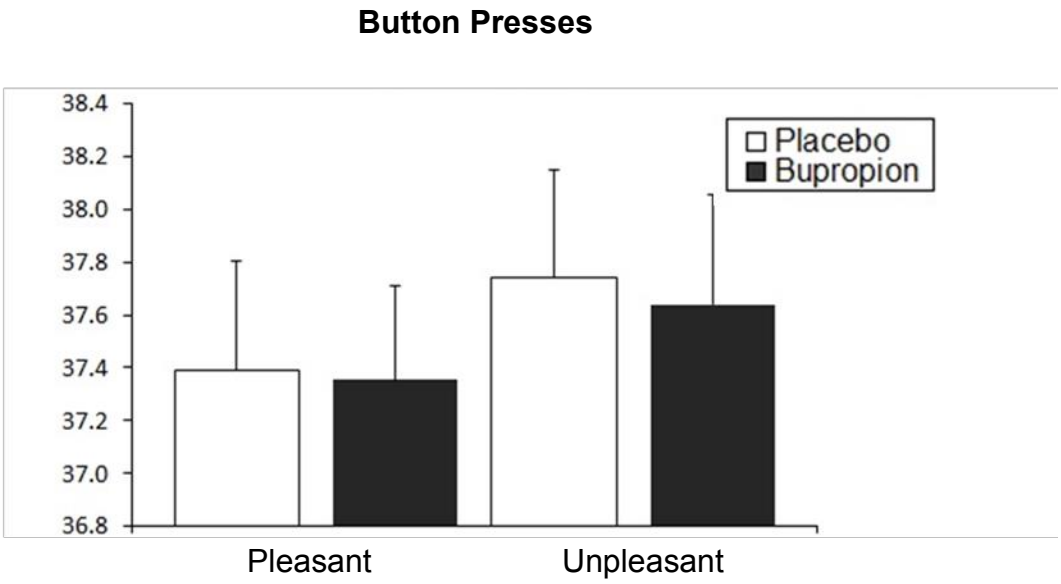
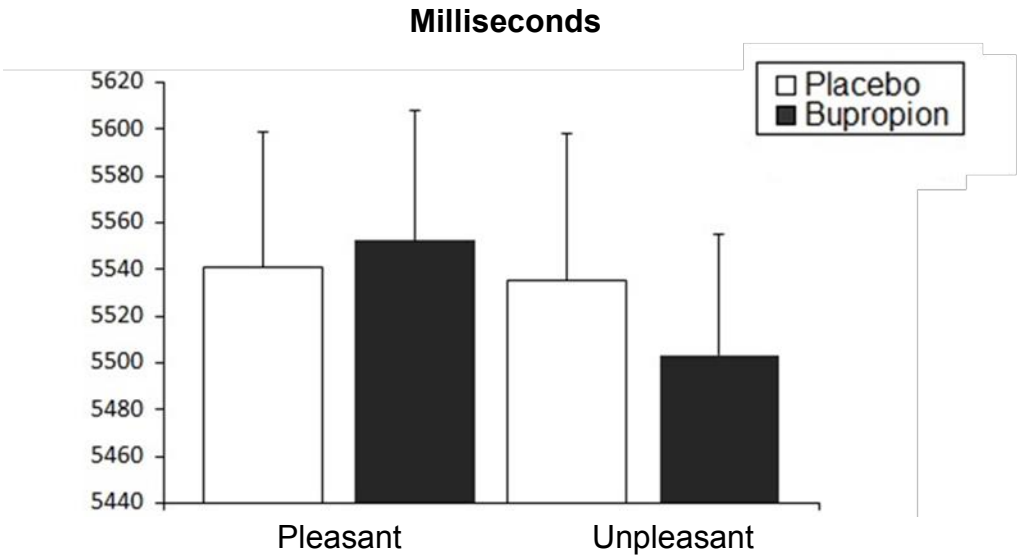


Figure S4. Average number of button presses and time taken to complete pleasant and unpleasant trials across bupropion and placebo conditions.





7.3. Supplementary Material: Paper 3

Increased Neural Response during the Anticipation and Effort to Avoid Aversion, but Not Reward, Following Agomelatine Treatment

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Figure S1. Visual depiction of a reward-hard trial.

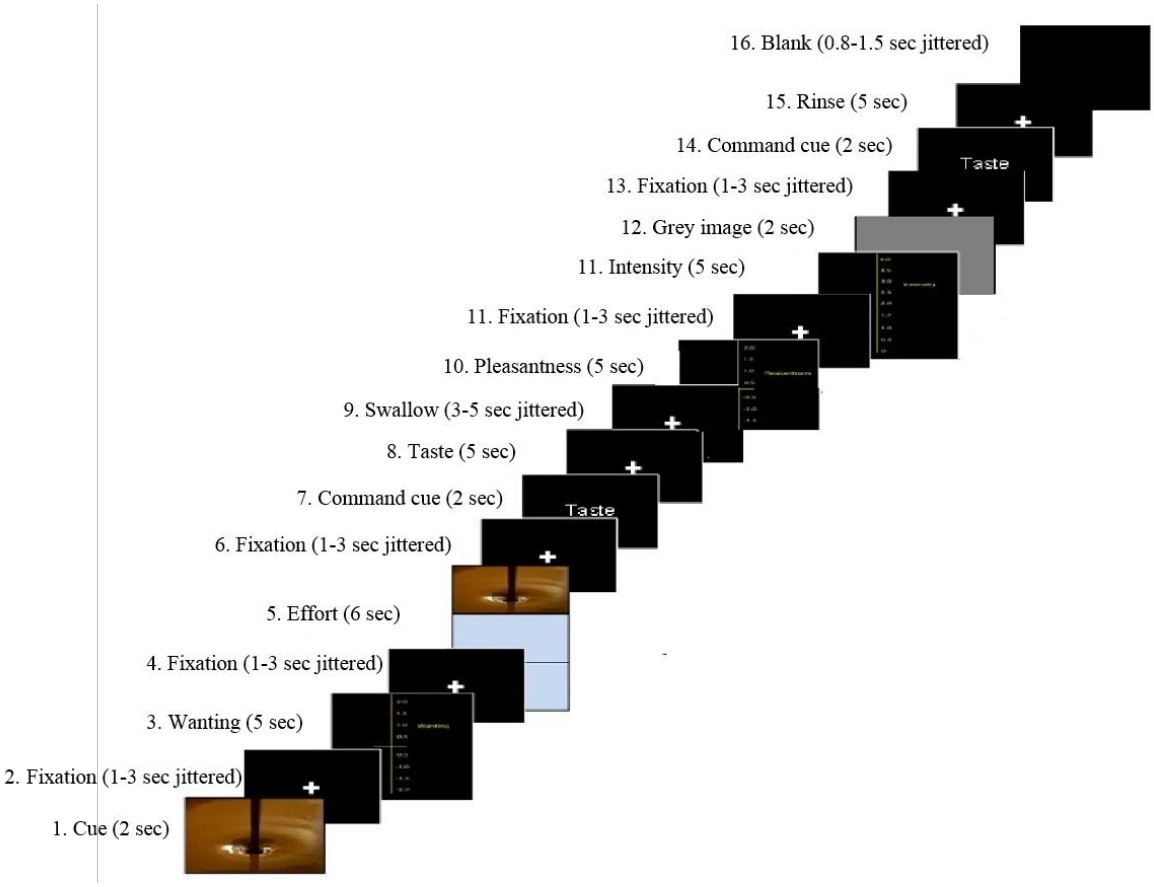


Table S1. Subjective state ratings pre- and post-treatment after 7 days of treatment with agomelatine and placebo, separated by a two-week washout phase. There were no significant effects of treatment condition on any of the measures.

Measure	Agomelatine Mean (SD)		Placebo Mean (SD)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
VAS				
Alertness	6.63 (2.51)	5.93 (2.48)	6.77 (1.86)	7.22 (1.93)
Disgust	0.50 (0.70)	0.34 (0.44)	0.80 (1.69)	0.47 (0.46)
Drowsiness	1.81 (1.77)	2.15 (2.35)	2.09 (2.56)	2.54 (2.66)
Anxiety	1.20 (1.34)	0.73 (0.94)	1.51 (2.08)	1.01 (1.41)
Happiness	7.67 (1.04)	7.23 (1.49)	7.52 (1.46)	7.87 (1.02)
Nausea	0.27 (0.24)	0.28 (0.26)	0.82 (1.95)	0.39 (0.41)
Sadness	0.76 (0.92)	0.79 (1.19)	0.82 (1.67)	0.55 (0.54)
Withdrawn	1.00 (1.11)	1.01 (1.49)	1.22 (2.00)	0.80 (1.46)
Faint	0.31 (0.29)	0.51 (0.58)	0.46 (0.47)	0.49 (0.64)
Total BFS score	11.00 (9.00)	10.00 (11.00)	12.00 (9.00)	12.00 (10.00)

SD, standard deviation; VAS, visual analogue scale (n=18); BFS, the Befindlichkeit Scale (n=17); Repeated measure analyses of variance; p>0.05.

Table S2. Frequencies of Adverse Effects Reported Under Agomelatine (*n*=18) and Placebo (*n*=18).

Adverse Event	Placebo	Agomelatine
Gastrointestinal symptoms		
Diarrhoea	1	0
Constipation	1	3
Dry Mouth	2	2
Nausea or vomiting	0	1
Heart symptoms		
Palpitations	0	0
Dizziness when standing	0	1
Chest pain	0	0
Skin symptoms		
Rash	0	1
Increase perspiration	0	
Itching	0	1
Dry skin	1	0
Nervous system symptoms		
Headache	3	3
Tremors	0	0
Poor coordination	0	0
Dizziness	0	0
Eye and ear symptoms		
Blurred vision	0	1
Ringing in the ears	0	1
Genital and urinary symptoms		
Difficulty urinating	0	0
Painful urination	0	0
Frequent urination	0	1
Menstrual irregularity	0	1
Sleep symptoms		
Difficulty sleeping	1	0

Sleeping too much	0	1
Sexual functioning		
Loss of sexual desire	0	0
Trouble achieving orgasm	0	0
Trouble with erections	0	0
Other symptoms		
Anxiety	0	0
Fatigue	0	1
Poor concentration	1	1
Decreased energy	0	1
General malaise	1	0
Restlessness	0	0
Other		
Stomach pain	1	0

Data are frequencies.

Table S3. Regions showing main effect of task irrespective of treatment for all subjects.

	MNI coordinates				
Brain region	X	Y	Z	Z score	Significance (*p* value*)*
Anticipatory[a]					
Chocolate cue – grey image					
Occipital pole	24	-94	16	6.83	<0.001
	-16	-98	6	6.71	<0.001
Postcentral gyrus	22	-40	70	4.71	0.012
vmPFC	10	52	2	4.29	0.003
pgACC	-2	38	10	4.14	<0.001
Unpleasant cue- grey image					
Occipital lobe	16	-84	-2	6.13	<0.001
	-14	-98	2	5.91	<0.001
Occipital fusiform gyrus	30	-48	-8	4.33	0.048
Lingual/parahippocampal gyrus	-22	-42	-10	4.25	0.033
Effort[b]					
Hard chocolate –easy chocolate					0.0001
Precentral gyrus	-32	-26	64	7.71	<0.001
lOFC/insula	36	22	-12	6.97	<0.001
Cerebellum	0	-60	-8	6.49	<0.001
dlPFC	28	56	30	5.28	<0.001
	-34	42	38	5.78	<0.001

Occipital lobe	-20	-98	10	5.70	<0.001
	10	-98	14	5.17	<0.001
Ventral striatum	4	6	-2	5.04	0.013
Middle Temporal gyrus	-46	-56	6	4.75	<0.001
Supracalcarine cortex	-24	-64	16	4.66	0.007
Caudate	14	26	0	4.59	0.017
Inferior frontal gyrus	60	14	20	4.45	0.044
Precuneous cortex	4	-66	18	4.37	0.002
Paracingulate gyrus	2	50	18	4.14	0.020
vmPFC	8	54	-6	3.71	0.029*
Hard unpleasant – easy unpleasant					
Precentral gyrus	-32	-30	50	6.96	<0.001
Operculum cortex	-58	-30	16	6.36	<0.001
	52	-30	24	4.67	<0.001
Occipital Pole	-26	-92	8	5.08	0.006
	26	-94	4	4.89	0.014
Frontal pole	-28	48	36	5.06	0.049
	30	52	36	4.75	0.012
Caudate	14	26	0	4.89	0.008
Easy unpleasant – hard unpleasant					
Middle Frontal gyrus	-38	22	26	4.79	0.015
Occipital lobe	-6	-88	12	4.18	0.010

Post/precentral gyrus	58	-8	32	4.13	0.015
Easy unpleasant – easy chocolate					
Occipital lobe	20	-94	0	6.05	<0.001
	26	-92	10	5.09	<0.001
Lingual gyrus	2	-66	-8	4.22	0.006
Hard chocolate – hard unpleasant					
Operculum cortex	38	6	12	3.90	0.049
Hard unpleasant – hard chocolate					
Occipital lobe	-26	-90	-4	6.18	0.001
	28	-94	8	6.05	0.002
Consummatory[b]					
Chocolate taste - rinse					
Precentral gyrus	-46	-28	62	5.75	<0.001
	-42	18	-10	4.70	0.002
lOFC/insula	44	22	-8	4.44	<0.001
	38	16	-12	4.36	<0.001
lPFC	44	46	0	4.08	<0.001
	-36	44	8	3.85	0.039
Unpleasant taste- rinse					
Precentral gyrus	-36	-28	58	5.74	<0.001
Superior	2	34	44	5.18	<0.001
Frontal/paracingulate gyrus					
dmPFC	10	60	22	5.17	<0.001
vlPFC	-34	50	-6	5.08	<0.001

lOFC/insula	-28	24	0	5.06	<0.001
	28	22	-10	4.39	0.004
Middle frontal gyrus	-48	30	30	4.92	0.004
	40	28	50	4.38	<0.001
Superior parietal lobule	-26	-54	44	4.77	0.014
Lateral occipital cortex	-26	-70	54	4.75	0.002
pgACC	2	52	8	4.27	0.006
Ventral striatum	-8	14	2	4.01	0.010*
Caudate	10	14	6	3.69	0.028*
mOFC	-4	40	-14	3.52	0.049*

MNI, Montreal Neurological Institute; vmPFC, ventral medial prefrontal cortex; pgACC, pregenual anterior cingulate cortex; lOFC, lateral orbitofrontal cortex; dlPFC, dorsal lateral prefrontal cortex; lPFC, lateral prefrontal cortex; dmPFC, dorsal medial prefrontal cortex; vlPFC, ventral lateral prefrontal cortex; mOFC, medial orbitofrontal cortex.

Data thresholded at [a] p =0.001 uncorrected [b] p =0.0001 uncorrected or * Region of Interest thresholded at p=0.05 uncorrected.

p values: Family Wise Error whole brain cluster corrected or * Family-wise error corrected at the peak voxel within the ROI.

Table S4. Regions showing parametric modulation by subjective ratings and effort during the anticipatory, effort and consummatory phases within placebo and agomelatine, separately.

	MNI coordinates				
Brain Region	X	Y	Z	Z score	Significance (*p* Value)
Anticipatory[a]					
Negative relationship with raw wanting ratings: agomelatine					
Postcentral gyrus	-40	-34	46	5.09	<0.001
Occipital fusiform gyrus	-22	-80	-14	4.53	0.002
Lingual gyrus	18	-82	0	4.34	<0.001
Operculum cortex	-34	10	20	3.92	0.035
Effort [b]					
Negative relationship with raw wanting ratings: placebo					
Lateral occipital cortex	-24	-90	-2	6.22	<0.001
	26	-92	8	4.89	<0.001
Negative relationship with raw wanting ratings: agomelatine					
Occipital pole	-18	-100	8	5.16	<0.001
	28	-90	0	4.46	<0.001

Cuneal cortex	-10	-70	18	4.70	<0.001
Midbrain	0	-30	-8	4.11	0.003
lOFC/Insula	28	24	-12	4.08	0.005
ACC	2	44	12	4.03	<0.001
Consummatory[c]					
Positive relationship with pleasantness ratings: placebo					
Superior Frontal gyrus	-16	36	56	4.25	<0.001
Precuneous cortex	0	-62	30	3.77	<0.001
Operculum cortex	50	-8	14	3.75	0.005
Angular gyrus	42	-50	24	3.65	0.004
Precentral gyrus	-4	-28	75	3.54	0.007
Lateral occipital cortex	-26	-72	56	3.32	0.032
Pre/postcentral gyrus	-58	-6	32	3.52	0.021*
Positive relationship with pleasantness ratings: agomelatine					
Post/precentral gyrus	18	-32	72	3.97	<0.001

MNI, Montreal Neurological Institute; bp/s, button presses per second; lOFC, lateral orbitofrontal cortex; ACC, anterior cingulate cortex.

No significant results for absolute wanting ratings at the anticipatory or effort phase.

Data thresholded at [a] p =0.005 uncorrected [b] p =0.001 uncorrected or [c] p =0.01 uncorrected * Region of Interest thresholded at p=0.05 uncorrected.

p values: Family Wise Error whole brain cluster corrected or * Family-wise error corrected at the peak voxel within the ROI.

Figure S2. Subjective pleasantness, wanting and intensity ratings of the pleasant and unpleasant stimuli in placebo and agomelatine conditions. There were no significant effects of treatment condition on any of the measures.

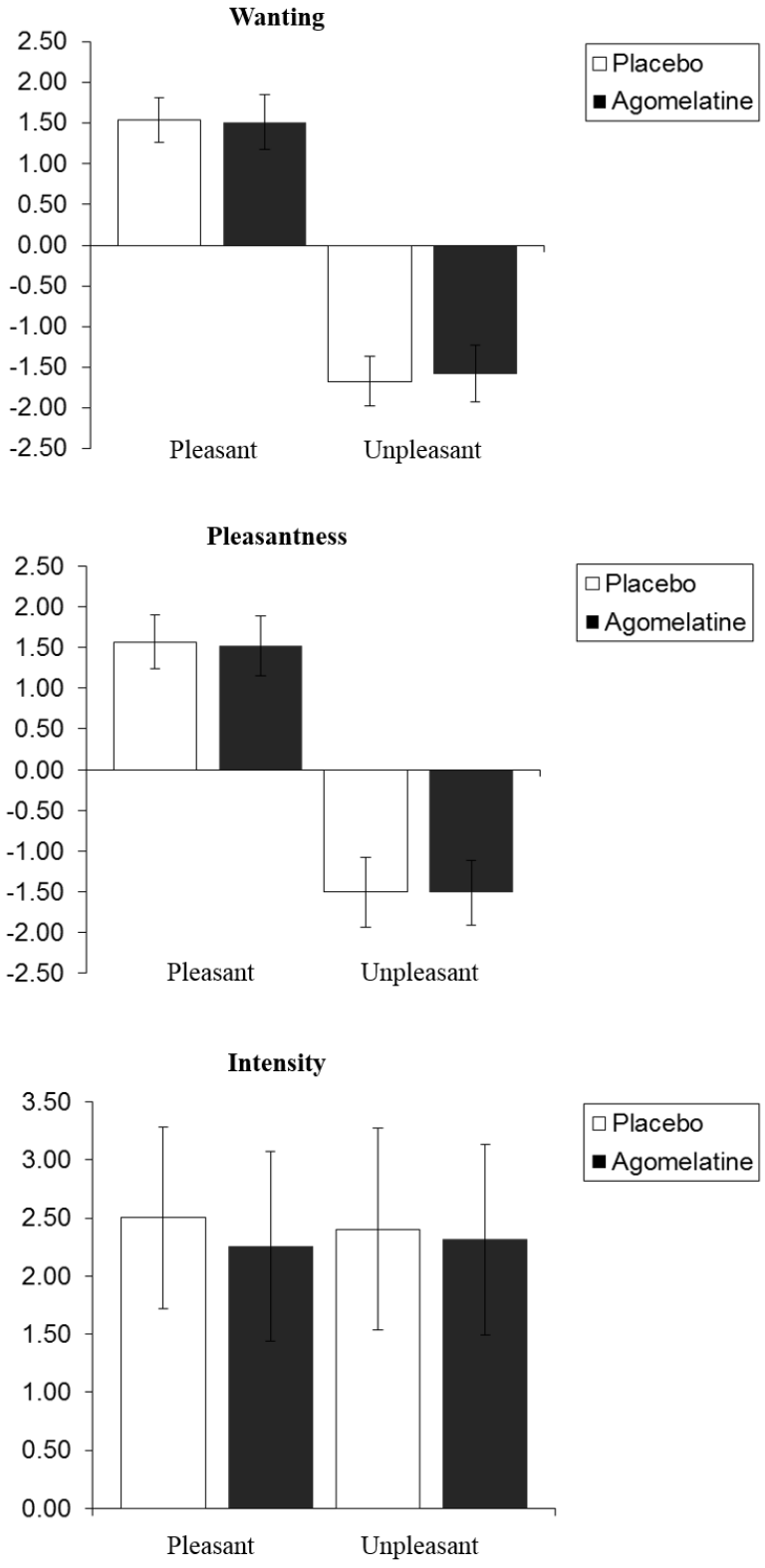
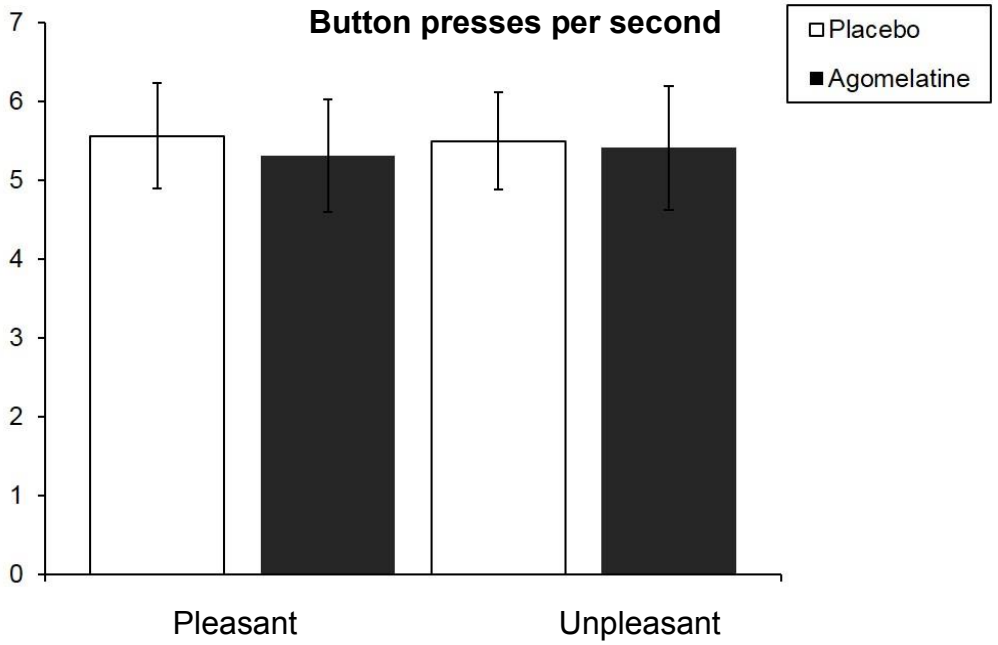
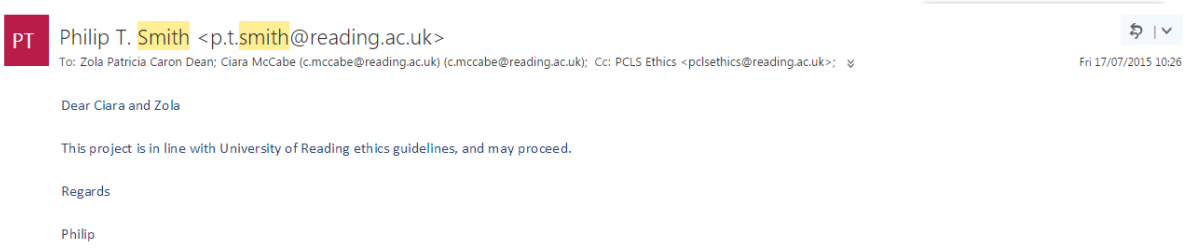


Figure S3. Average number of button presses per second made on pleasant and unpleasant trials across agomelatine and placebo conditions.



7.4. Ethical approval for paper 1



PT Philip T. Smith <p.t.smith@reading.ac.uk>

To: Zola Patricia Caron Dean; Ciara McCabe (c.mccabe@reading.ac.uk) (c.mccabe@reading.ac.uk); Cc: PCLS Ethics <pclsethics@reading.ac.uk>;

Fri 17/07/2015 10:26

Dear Ciara and Zola

This project is in line with University of Reading ethics guidelines, and may proceed.

Regards

Philip

7.5. Ethical approval for paper 2

University of Reading

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Dr Clara McCabe
School of Psychology and Clinical Language Sciences
University of Reading
RG6 6AL

27 April 2014

Dear Clara

UREC 14/13: UREC 14/19: 2014-006-CM - Effect of 7 days of bupropion (150mg) vs. placebo on Neural Reward Processing in Healthy human volunteers. *Favourable opinion*

Thank you for your email dated 27 March addressing the points raised by the UREC Sub-committee. I can confirm that the Chair is pleased to confirm a favourable ethical opinion on the basis of the changes you have made and the information you have supplied. I note your intention to include two psychiatrists from the Berkshire Healthcare NHS Foundation Trust as researchers on this study and will be happy to receive the revised documentation (for amendment as Chair's action) in due course.

Please note that the Committee will monitor the progress of projects to which it has given favourable ethical opinion approximately one year after such agreement, and then on a regular basis until its completion.

Please also find attached Safety Note 59: Incident Reporting in Human Interventional Studies at the University of Reading, to be followed should there be an incident arising from the conduct of this research.

The University Board for Research and Innovation has also asked that recipients of favourable ethical opinions from UREC be reminded of the provisions of the University Code of Good Practice in Research. A copy is attached and further information may be obtained here: http://www.reading.ac.uk/internal/res/QualityAssuranceInResearch/reas-RSqar.aspx.

Yours sincerely

Dr M J Proven
Coordinator for Quality Assurance in Research (UREC Secretary)
cc: Dr John Wright (Chair); Dr Laurie Butler; Dr Stephanie Horndasch

7.6. Ethical approval for paper 3

University of Reading

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Dr Clara McCabe
School of Psychology and Clinical Language Sciences
University of Reading
RG6 6AL

15 July 2015

Dear Clara

UREC 15/39: The effects of agomelatine on neural responses to reward and aversion in healthy volunteers. *Favourable opinion*

Thank you for the application (email dated 19 June 2014, from Zola Dean and including attachments refers). On the basis of these documents I can confirm that the Chair is pleased to confirm a favourable ethical opinion.

Please note that the Committee will monitor the progress of projects to which it has given favourable ethical opinion approximately one year after such agreement, and then on a regular basis until its completion.

Please also find attached Safety Note 59: Incident Reporting in Human Interventional Studies at the University of Reading, to be followed should there be an incident arising from the conduct of this research.

The University Board for Research and Innovation has also asked that recipients of favourable ethical opinions from UREC be reminded of the provisions of the University Code of Good Practice in Research. A copy is attached and further information may be obtained here:

http://www.reading.ac.uk/internal/res/QualityAssuranceInResearch/reas-RSqar.aspx

Yours sincerely

Dr M J Proven
Coordinator for Quality Assurance in Research (UREC Secretary)
cc: Dr John Wright (Chair); Professor Laurie Butler (Head of School); Zola Dean (PhD student)

NHS
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Telephone: (0117) 3421382

22 May 2015

Dr Ciara McCabe
School of Psychology and Clinical Language Sciences
University of Reading
Reading RG6 6AL

Dear Dr McCabe

Study title:	**The effects of agomelatine on neural responses to reward and aversion in healthy volunteers.**
REC reference:	**15/SC/0229**
IRAS project ID:	**174605**

Thank you for your letter of 27 April 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Assistant, Mr Wai Yeung, nrescommittee.southcentral-berkshireb@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster]	1	23 March 2015
Interview schedules or topic guides for participants [Medial history interview]	1	23 March 2015
Interview schedules or topic guides for participants [Brief Psychiatric interview]	1	23 March 2015
IRAS Checklist XML [Checklist_31032015]		31 March 2015
IRAS Checklist XML [Checklist_27042015]		27 April 2015
Non-validated questionnaire [Demographic details]	1	23 March 2015
Non-validated questionnaire [VAS]	1	23 March 2015
Non-validated questionnaire [MRI Initial screening form]	1	16 March 2015
Other [Response letter]		27 April 2015
Other [Amended Protocol]	2	27 April 2015
Other [Revised blood consent]	2	27 April 2015
Other [Amended PIS]	2	27 April 2015
Other [Amended medical interview]	2	27 April 2015
Other [Amended Online Questionnaires]	2	27 April 2015
Participant consent form [Study consent]	1	23 March 2015
Participant consent form [Bloods consent]	1	23 March 2015
Participant information sheet (PIS)	1	23 March 2015
Participant information sheet (PIS) [General MRI Information]	1	23 March 2015
REC Application Form [REC_Form_31032015]		31 March 2015
Research protocol or project proposal [Ago_Protocol_NHS]	1	20 February 2015
Summary CV for Chief Investigator (CI)	1	16 March 2015
Summary CV for student [Zola Dean & Alexandra Antonesei summary CVs]	1	16 March 2015
Summary, synopsis or diagram (flowchart) of protocol in non technical language	1	23 March 2015
Validated questionnaire [FCPS, BDI, EAT, SHAPS, TEPS, BIS/BAS]	1	23 March 2015
Validated questionnaire [NART]	1	23 March 2015
Validated questionnaire [Side effects qaire]	1	16 March 2015
Validated questionnaire [BFS]	1	23 March 2015
Validated questionnaire [Chocolate cravings]	1	23 March 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance

on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/SC/0229	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

Mr Wai Yeung
Research Ethics Committee (REC) Assistant

pp Dr John Sheridan – Chair of South Central - Berkshire B REC

Email:nrescommittee.southcentral-berkshireb@nhs.net

Enclosures: "After ethical review – guidance for researchers"

7.7. Beck Depression Inventory-II (BDI)

The BDI measures to what degree a respondent is experiencing 21 symptoms related to depression. Each item is responded on a 0-3 scale, with higher values indicating greater symptom severity (minimum 0, maximum 63) (Beck, Steer, & Brown, 1996).

7.8. Eating Attitudes Test (EAT)

The EAT is a 26-item questionnaire that measures concerns regarding weight-gain and eating calorific foods. Each item is responded using a 6-item scale (always, usually, often, sometimes, rarely and never). The minimum possible score is 0 and the maximum possible is 78, with higher scores signifying greater worries about gaining weight and consuming calorific food (Garner, Olmsted, Bohr, & Garfinkel, 1982).

7.9. Snaith-Hamilton Pleasure Scale (SHAPS)

The SHAPS is a 14-item questionnaire that aims to measure consummatory pleasure by asking respondents to what degree they agree or disagree that they would experience pleasure to a given situation, based on how they have felt in the past few days. Each item is responded using a 4-item scale (definitely agree, agree, disagree, and definitely disagree). The minimum possible score is 14 and the maximum possible is 56, with higher scores representing greater deficits in experiencing pleasure (greater consummatory anhedonia) (Snaith et al., 1995).

7.10. Temporal Experience of Pleasure Scale (TEPS)

The TEPS is an 18-item questionnaire that aims to measure anticipatory (10 items, min score 10, max score 60) and consummatory (8 items, min score 8, max score 48) pleasure. Questions measuring consummatory pleasure ask respondents to indicate how accurate a statement applies to them, in terms of whether they enjoy a given situation. The anticipatory subscale asks respondents to indicate how accurate a statement applies to them, in terms of whether they 'look forward' to different activities. Each item is responded using a 6-item scale (very false for me, relatively false for me, somewhat false for me, somewhat true for me, relatively true for me and very true for me). Two versions exist, one asking responses to be made based on how the respondent generally feels (trait) and the other based on how they have felt in the past week (state). Lower scores represent

greater deficits in experiencing pleasure (greater consummatory anhedonia) (Gard, Kring, Gard, Horan, & Green, 2007).

7.11. Behavioural Inhibition/Activation Scales (BIS/BAS)

The BIS/BAS is a 24-item questionnaire measuring negative affective responses (e.g. worry) to given situations (BIS, 7 questions, min score 7 max score 28) and three subcomponents are related to appetitive motivation 1) BAS drive (4 questions, min score 4, max score 16), 2) BAS fun seeking (4 questions, min score 4, max score 16), and 3) BAS reward responsiveness (5 questions, min score 5 max score 20). Each item is responded using a 4-item scale (very true for me, somewhat true for me, somewhat false for me and very false for me). Higher scores on the BIS indicate less negative affective response to negative scenarios and higher scores on the BAS scores signify greater drive, fun seeking and reward responsiveness (Carver & White, 1994).

7.12. Fawcett-Clarke Pleasure Capacity Scale (FCPS)

The FCPS is a 36-item questionnaire that aims to measure consummatory pleasure by asking respondents to indicate to what degree they would experience pleasure to a given situation. Each item is responded using a 5-item scale (no pleasure at all, mild pleasure, moderate pleasure, great pleasure, extreme and lasting pleasure). The minimum possible score is 36 and the maximum possible is 180, with lower scores representing greater deficits in experiencing pleasure (greater consummatory anhedonia) (Fawcett, Clark, Scheftner, & Gibbons, 1983).

7.13. Visual Analogue Scale (VAS)

Mood and physiological state (e.g. happiness and alertness) were measured using visual analogue scales (VAS). Respondents indicated to what degree they felt a given mood or physiological state by placing a mark along a 10cm line (0 completely absent, 10 the most they could ever imagine) (Bond & Lader, 1974). A VAS was also used to measure how hard volunteers felt they worked during the task in paper 1 (0 not very much, 10 very much). Using a ruler, a value between 0-10 was obtained, with higher scores representing that the respondent felt ‘more’ of this emotion.

7.14. Befindlichkeit Scale of mood and energy (BFS)

The BFS is a 56–item questionnaire that presents respondents with a pair of words describing an emotion/mood state in opposite directions (e.g. alert versus listless). Respondents are asked to indicate which of the two words best describes their current mood, or they can mark 'neither-nor' if more appropriate. Higher scores on this questionnaire indicate a more negative current mood (von Zerssen, Strian, & Schwarz, 1974).

7.15. Barratt Impulsiveness Scale (BIS-11)

The BIS-II is a 30-item questionnaire that measures how impulsive a respondent is. Each item is responded using a 4-item scale (rarely/never, occasionally, often and almost always/always). The minimum possible score is 30 and the maximum possible is 120, with higher scores signifying greater impulsivity (Patton, Stanford, & Barratt, 1995).

7.16. State-Trait-Anxiety Inventory-Y2 (STAI)

We used the trait version of the STAI, which measures how respondents generally feel in relation to anxiety symptoms, using 20-items. Each item is responded using a 4-item scale (almost never, sometimes, often and almost always). The minimum possible score is 20 and the maximum possible is 80, with higher scores signifying greater symptoms of anxiety (Spielberger, 1983).

7.17. Monetary Choice Questionnaire (MCQ)

The MCQ asks respondents to indicate if they would prefer to receive a smaller amount of money today or a larger amount of money in the future. Higher scores indicate a stronger preference for immediate rewards (Kirby, Petry, & Bickel, 1999). Scores were calculated using an automated spreadsheet (Kaplan, Lemley, Reed, & Jarmolowicz, 2014).

7.18. Patient Rated Inventory of Side Effects to record any adverse side-effect (PRISE)

The PRISE asks respondents to indicate what symptoms they have experienced in the past week, and whether they were tolerable or distressing, using a tick-box method. Nine categories are assessed; gastrointestinal, nervous system, heart, eyes/ears, skin,

genital/urinary, sleep, sexual dysfunction, other (e.g. anxiety and fatigue) (Rush et al., 2004).

7.19. DSM-IV Structured Clinical Interview (SCID)

The SCID is an interview schedule used to diagnose mental health disorders. A brief version of the DSM-IV was used to interview participants regarding current and previous experiences related to Axis I disorders (Spitzer, Williams, Gibbon, & First, 2004).

7.20. Chocolate questionnaire

This questionnaire measures how much respondents crave and like chocolate (1-10, with higher values signifying more), as well as how frequently, and how much, they consume chocolate. The questionnaire also measures how much respondents like milk and whether they crave any other foods and to what degree (0-10 scale) (Rolls & McCabe, 2007).

7.21. References

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