PARSING ANHEDONIA: EFFORT-BASED DECISION-MAKING AS A TRANSLATIONAL MODEL OF MOTIVATIONAL DEFICITS IN MAJOR DEPRESSIVE DISORDER

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To my mother, whose curiosity and sense of wonderment taught me how to ask

and

To my father, whose unflinching compassion taught me how to listen

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ABSTRACT

Major Depressive Disorder (MDD) is a persistent, severe mental disorder with approximately 16% lifetime prevalence. Anhedonia has long been recognized as a core feature of the disorder. Described as a reduction in the interest or enjoyment derived from pleasurable activities, clinical assessment of anhedonia has primarily relied on clinician-rated or self-reported hedonic responses to past experiences or laboratory stimuli, despite the well-established clinical observation that anhedonia is often accompanied by reductions in motivation. The lack of attention to possible motivational deficits in anhedonia has hindered efforts to uncover the pathophysiology of this debilitating symptom, as substantial preclinical evidence suggests that motivational and consummatory aspects of reward processing possess distinct neurobiological substrates. In particular, the mesocorticolimbic dopamine (DA) system has long been hypothesized to play a role in the pathophysiology of anhedonic symptoms, but empirical validation of this hypothesis has remained elusive. In this dissertation, I suggest that the lack of a clear demonstration of DA dysfunction in anhedonic depression may result from the reliance on measures of anhedonia that primarily emphasize the subjective experience of pleasure, while preclinical data strongly implicate DA in primarily motivational aspects of reward processing. To address this issue, I introduce a novel behavioral measure that may be used to address motivational deficits in patient populations experiencing anhedonia. Dubbed the Effort Expenditure for Rewards Task (EEfRT or “effort”), this measure was adapted

from preclinical effort-based decision-making paradigms that have been successfully used to demonstrate the role of DA function in determining an organism's willingness to expend physical effort in pursuit of a given reward. Over three empirical studies, I demonstrate that the EEfRT is sensitive to individual differences in reward motivation, which are in turn linked to anhedonic traits, human DA function and clinical depression. The results of these studies offer novel insights into the neurobiological mechanisms underlying motivational aspects of anhedonic symptoms, with important implications for future treatment and prevention.

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Introduction

With a lifetime prevalence of approximately 16% (Kessler, et al., 2003), Major Depressive Disorder (MDD) is predicted to become the second leading cause of death and disability in the United States by the year 2020 (Murray & Lopez, 1997). Dating back to the original Feighner criteria published in 1972, anhedonia has long been presumed as a core feature of MDD (Feighner, 1972). The DSM-IV-TR (American Psychiatric Association, 1994) defines anhedonia as diminished interest or pleasure in response to stimuli that were previously perceived as rewarding during a pre-morbid state (DSM-IV-TR). Along with depressed mood, anhedonia is one of two required symptoms for a diagnosis of MDD (APA, 1994). Recent reports estimate that approximately 37% of individuals diagnosed with MDD experience clinically significant anhedonia (Pelizza & Ferrari, 2009). Moreover, prior studies indicate that anhedonia predicts depressive symptoms (Hundt, Nelson-Gray, Kimbrel, Mitchell, & Kwapil, 2007) time to recovery (McFarland, Shankman, Tenke, Bruder, & Klein, 2006), and poor treatment outcomes (Kasch, Rottenberg, Arnow, & Gotlib, 2002; McFarland, et al., 2006 ; Spijker, Bijl, de Graaf, & Nolen, 2001). Anhedonia is also a particularly difficult symptom to treat as accruing evidence suggests that current first-line pharmacotherapies (e.g., SSRIs) do not adequately address motivational and reward-processing deficits in depression (APA, 2000; Dunlop & Nemeroff, 2007; McCabe, Cowen, & Harmer, 2009; Nutt, et al., 2007; Price, Cole, & Goodwin, 2009; Shelton & Tomarken, 2001).

The Challenge of Heterogeneity in Major Depressive Disorder

For several decades now, popular culture has likened the psychiatric diagnostic construct of Major Depressive Disorder (MDD or “depression”) as being akin to medical diagnosis of fever; both possess several clearly identifiable, surface-level features that belie a myriad possible culprits. Like fever, the causes of MDD are too varied and individual that the diagnosis offers little informational value in terms of guiding treatment and prevention. In an effort address this problem, a longstanding goal of the National Institute of Mental Health has been to identify their biological basis. Since the earliest biological accounts of depressive symptomatology (Schildkraut, 1965), researchers have consistently identified disturbances in a wide range of biological systems when comparing MDD patients with healthy controls, including multiple classes of neurotransmitters (monoamines, GABA, glutamate) (Gabbay, et al., 2012; Owens & Nemeroff, 1994; Pittenger, Sanacora, & Krystal, 2007; Sanacora, et al., 2004; Walter, et al., 2009), endocrine systems (Holsboer, 2000), immune systems (Miller, Maletic, & Raison, 2009), neurotrophin systems (Duman & Monteggia, 2006), region-specific functional and structural alterations and patterns of functional connectivity (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005a; Pizzagalli, et al., 2009; Sheline, Price, Yan, & Mintun, 2010). These effects have proven to be stable and robust, as determined by multiple meta-analyses (Fitzgerald, Laird, Maller, & Daskalakis, 2008; Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009). Despite this wealth of positive findings, however, none of these biological systems appear to show

strong enough specificity for the disorder. That is to say, while *mean* differences between depressed and non-depressed samples emerge consistently, it is invariably a subset of patients in each study that account for the overall group difference (Raison & Miller, 2011). Consequently, we have yet to uncover a single biological process that can accurately be described as being *necessary* for the MDD symptomatology.

Two basic conclusions can be drawn from this substantial body of work. The first is that MDD is unquestionably a biological disorder, this is true despite persistent notions that depression is "caused" by intuitively appealing factors, such as recent losses and stressors (Kendler, 2012; Kendler, Myers, & Halberstadt, 2011). The second is that the biological basses of depression may be so heterogeneous that the MDD construct is of little use for the purposes of studying underlying biological mechanisms (Hyman, 2002, 2010). This is true not only in regards to the presence or absence of specific symptoms within a disorder (diagnostic heterogeneity), but also for the presence or absence of co-morbid conditions (heterogeneity of co-morbidity), etiological pathways involved in disorders (etiological heterogeneity).

Attention to these multiple forms of heterogeneity has proven critical for elucidating the neurobiological pathways involved. For example, under the DSM-IV definition of a Major Depressive Episode, there are 126 unique combinations of symptoms possible, with two MDD positive individuals sharing only a single symptom of the disorder. Such heterogeneity in how an individual meets criteria may be both practical and theoretically appropriate, but it may also mask

important associations that are related to specific symptoms, rather than the whole diagnostic category. Similarly, co-morbidity may obscure disorder-specific, or symptom-specific associations. For instance, while multiple studies have shown that individuals with depression exhibit increased amygdala activation in response to negatively-valenced stimuli (Fu, et al., 2004; Siegle, Carter, & Thase, 2006; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007), newer evidence suggests that this amygdala activity may occur primarily in individuals with MDD and co-morbid anxiety symptoms (Beesdo, et al., 2009). Heterogeneity in etiological factors may also be important. In testing the role of the Hypothalamic-Pituitary-Adrenal (HPA) Axis in MDD, it has been demonstrated that individuals with depression and early life-trauma exhibit structural reductions in regions involved in HPA axis regulation, while individuals with depression but not early-life trauma do not (Treadway, Grant, et al., 2009; Vythilingam, et al., 2002). In sum, the use of case-control designs to uncover the pathophysiological mechanisms underlying the symptoms of MDD that ignore this type of etiological heterogeneity may conceal important neurobiological differences (Heim, Plotsky, & Nemeroff, 2004).

Confronting Heterogeneity: Anhedonia Fever

One solution to this problem has been to focus on identifying the biological basis of specific symptoms within MDD, with the hypothesis that individual symptoms would show less heterogeneity than the disorder as a whole (Hasler, Drevets, Manji, & Charney, 2004). Reward-related symptoms represent an

excellent opportunity for this type of translational neuroscience approach, given the vast basic science literature from which to draw upon (Berridge & Robinson, 2003; Gold et al., 2008). However, application of this important preclinical work to human conditions is hampered by the enormous heterogeneity in symptom presentation. As with the diagnostic category of MDD as a whole, individual symptoms exhibit significant variability in their specific nature, which are often difficult to assess using standard self-report and clinician-rated assessments. While less commonly acknowledged than the above-mentioned forms of heterogeneity, symptom heterogeneity represents an additional barrier to the identification of biological substrates that can lead to causal explanations.

In the case of anhedonia, the DSM-IV-TR states that individuals meeting criteria "may report feeling less interest in hobbies, 'not caring anymore,' or not feeling any enjoyment in activities that were previously considered pleasurable" (American Psychiatric Association, 1994, p. 349). In other words, clinical diagnosis of anhedonia does not discriminate between a decrease in motivation and a reduction in experienced pleasure. The failure to draw such a distinction may reflect the long-held assumption that people are motivated to pursue the things they find pleasurable, and vice-versa. More critically, it suggests that the analogy of fever may be applicable even at the symptom-level, where anhedonia emerges as a syndrome within itself with multiple etiologies and pathophysiological mechanisms.

Symptom-level Heterogeneity and the Neurobiology of Anhedonia

In this dissertation, I argue that heterogeneity at the level of symptom definition is at least as problematic as the more commonly acknowledged issues of co-morbidity or etiological variability in MDD as a whole. In making this argument, I suggest that the distinction between the motivational and hedonic aspects of anhedonia is critical, especially when attempting to elucidate neurobiological pathways underlying the expression of this symptom. Indeed, overly broad definitions may sometimes point towards spurious relationships between symptom and substrate. For example, early models of anhedonia posited a central role for the monoamine neurotransmitter dopamine (DA) (Willner, 1983a, 1983b, 1983c), given preclinical evidence suggesting that DA mediated an organism's experience of pleasure in response to rewarding stimuli (Wise, 1980). In the intervening quarter-century however, only half of this original hypothesis has found empirical support. Namely (and as described in Chapter III), subsequent research using neuroimaging, pharmacological and genetic methods in both humans and animals has provided some support for the claim that DA function is impaired in at least a sub-population of individuals with MDD (Dunlop & Nemeroff, 2007; Yadid & Friedman, 2008). However, contrary to the original anhedonia hypothesis, the conceptualization of DA as being primarily related to pleasure has been largely abandoned (Berridge & Robinson, 2003; Salamone, Correa, Farrar, & Mingote, 2007).

These two developments raise a potential problem: if alterations in DA are a significant component in the pathogenesis of MDD but are unrelated to deficits

in experience of pleasure, what is their functional and clinical consequence? While it is often assumed that these processes are tightly coupled at both the biological and phenomenological level, preclinical data on the biological bases of reward processing has largely challenged this view. Indeed, expanding off the work of Berridge and others, one could plausibly sub-divide the anhedonia construct in terms of deficits in the hedonic response to rewards ("consummatory anhedonia") and a diminished motivation to pursue them ("motivational anhedonia"), which can be seen as roughly corresponding to the reward-processing components of 'liking' and 'wanting" proposed in the preclinical literature (Berridge & Robinson, 1998, 2003). These distinctions have been largely overlooked in the extant empirical literature on MDD, which may explain why this literature is replete with inconsistent findings (Forbes, 2009).

This strategy is not entirely new, and indeed echoes decades-old theoretical models and clinical observations. Neurobiological models of personality have previously emphasized dissociations between "approach" and "consumption" of rewards, with the former constituting a behavioral activation system. These models further posited that DA is primarily linked with approach emotions, and might therefore underlie individual differences in reward seeking behaviors and psychopathology (Cloninger, 1987; Depue & Collins, 1999; Depue & Iacono, 1989; Gray, 1987). Similarly, this dissociation has been noted in the clinical literature; the psychiatrist Donald Klein noted that many patients with depression and anhedonia appeared to enjoy rewards that were readily available, yet complained bitterly about feeling no desire to obtain them (Klein,

1987). However, there has yet to be rigorous, objective approach to the exploration of motivational deficits in MDD, and their neurobiological underpinnings.

The goal of this dissertation is to provide such an approach. To accomplish this objective, the studies described herein have focused on the development and validation of a translational experimental paradigm that can be used to objectively assess reward motivation in humans. Using this measure, these studies proceed to explore the personality and neurochemical correlates of individual differences in reward motivation, and their relevance to MDD.

Specific Aims

Specific Aim 1: Design and validate a translation measure of effort-based decision-making for use in humans

The goal of this aim was to design a behavioral measure that would be sensitive to individual differences in effort-based decision-making in humans, and that would parallel tasks used in the animal literature closely enough to facilitate translational approaches to testing hypothesis of neurobiological mechanisms. Chapters II and III of this dissertation provide a review of clinical and preclinical studies that informed the rationale and design considerations for this measure, and Chapter IV presents data from a pilot study focused on providing initial validation of the finalized task design.

Specific Aim 2: Explore the role of DAergic circuitry in human effort-based decision-making

One of the primary motivating factors for the translation of an effort-based decision-making paradigm from animals to humans has been to specifically explore the role of DA as neurochemical substrate of motivation. Chapter V of this dissertation describes a study relating individual differences in effort-based decision-making in humans to variability in mesocorticolimbic DA function. DA function was assessed in this study using PET imaging of D2/D3 receptor availability both on and off a *d*-amphetamine challenge paradigm.

Specific Aim 3: Examine the presence of effort-based decision-making deficits in MDD

Having developed an experimental paradigm that is successfully modeled after effort-based decision-making studies in animals (Aim 1), and demonstrating its ability to translate preclinical models of DA function (Aim 2), the goal of Aim 3 was to explore behavioral performance on this measure in a clinical sample. As described in Chapter VI, a sample of MDD patients and matched healthy controls were compared to test the hypothesis that MDD patients (or at least a subset of them) would exhibit less willingness to work for rewards.

CHAPTER II

ASSESSMENT OF ANHEDONIA IN MDD

As outlined in the introduction, the guiding hypothesis of this dissertation is that anhedonia is a complex symptom with multiple manifestations, etiologies, and pathophysiological mechanisms, all of which carry significant implications for treatment and prevention. To address this problem, I have recommended the division of anhedonia into motivational and consummatory sub-components. In this chapter, I provide a review of clinical studies of anhedonia in MDD that provide the basis for this proposal.

Diagnosis of Anhedonia in MDD

According to the current DSM-IV, anhedonia is one of two symptoms required for a diagnosis of MDD, the other being dysphoric mood (APA, 1994), suggesting that anhedonia is a "core feature" of the disorder. This requirement would imply that as compared to the other 8 symptoms of MDD, the presence or absence of anhedonia should have greater sensitivity and specificity for an MDD diagnosis than other symptoms, such as appetite disruption. However, the psychometric properties of symptoms in MDD have only recently been subjected to rigorous empirical analysis. Beginning in 2006, the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project published a series of papers exploring the psychometric aspects of DSM criteria as assessed using a structured interview in a sample of 1523 subjects (Zimmerman,

McGlinchey, Young, & Chelminski, 2006). As part of this study, they also made head-to-head comparisons between current DSM-IV symptom criteria and theoretical criteria, such as helplessness/hopelessness, lack of emotional reactivity, and diminished drive (a construct similar to motivational anhedonia). This additional diminished drive criterion is distinct from the typical Structural Clinical Interview for DSM Axis-I Disorders (SCID) assessment of anhedonia, which does not dissociate between motivational or consummatory aspects of reward; in keeping with DSM-IV criteria, the SCID simply asks patients whether they “have lost interest or pleasure in things that they usually enjoy”. Strikingly, diminished drive in combination with reported loss of energy criterion had the second highest odds-ratio for predicting a diagnosis of depression (50.1), ranking only below sad mood (61.2) and significantly greater than anhedonia as assessed by the SCID (29.7) (McGlinchey, Zimmerman, Young, & Chelminski, 2006). This finding is all the more impressive when considering the fact that the criterion of diminished drive is handicapped in comparison to the DSM anhedonia criteria, as only the latter bears directly on diagnostic outcome. While these results support the designation of anhedonia as reflecting a core feature of MDD, it also highlights the importance of motivation and drive, as compared to the standard assessment item that does not discriminate between motivational and consummatory aspects of this symptom.

Dimensional Assessment: Self-Report Measures

Dimensional assessment of anhedonic symptom severity has primarily been achieved through self-report instruments. A content review of items used in the most common anhedonia measures reveals that they unanimously emphasize the experience of pleasure in response to positive stimuli, with little or no attention to diminished drive or motivation. This includes the Chapman Anhedonia Scale (Chapman, Chapman, & Raulin, 1976), the Scale of Negative Symptoms (SANS; (Andreasen, 1982), the Fawcett-Clark Pleasure Scale, (FCPS; (Fawcett, Clark, Scheftner, & Hedeker, 1983) and the Snaith-Hamilton Pleasure Scale (SHAPS; (Snaith, et al., 1995). It is also worth noting that several of these scales were developed with a primary focus on schizophrenia (Chapman, SANS) rather than depression. Symptom severity instruments specific to depression often assess anhedonia with a small number of items; a single question in the case of the 17-item Hamilton Depression Rating Scale (Hamilton, 1960), two items on the 21-item Beck Depression Inventory (BDI anhedonia scale; (Beck, Steer, Ball, & Ranieri, 1996)) and four on the 30-item Inventory of Depressive Symptoms. Importantly, none of these scales have made an explicit attempt to dissociate between pleasure and motivational aspects of anhedonia. More recently, the Temporal Experience of Pleasure Scale (TEPS; (Gard, 2006) was developed to assess anticipatory and consummatory pleasure. This scale is a promising advance, though it is unclear whether the experience of pleasure when anticipating rewards is an identical construct to reward motivation,

and its application in MDD patient populations will be necessary to determine its utility for parsing clinical anhedonia.

In seeking to assess the relevance of these commonly used anhedonia assessment inventories, one recent study used a 10-indicator, 3-factor confirmatory factor analysis model to assess multiple measures of depression and anhedonia in a sample of controls and individuals with MDD. Anhedonia questionnaires included the Chapman, FCPS, and SHAPS, as well as clinical symptom inventories (BDI and Beck Anxiety Inventory; BAI). Using this approach, they identified three latent variables reflecting hedonic capacity, depressive symptoms and anxiety symptoms, and found that the hedonic capacity and depression variables were only moderately associated (factor loading = -0.20) (Leventhal, Chasson, Tapia, Miller, & Pettit, 2006).

Finally, the Mood-Anxiety Symptoms Questionnaire (MASQ) developed by Watson and Clark (Watson, Clark, et al., 1995; Watson, Weber, et al., 1995), includes a number of items related to lowered positive affect and interest, some of which appear related to aspects of anhedonia. However, these items are generally not treated separately from the larger scales that contain them, which remain relatively heterogeneous. Therefore, collapsing across these different forms of reward deficits may obfuscate the results, and may contribute to weaknesses in fitting a three-factor model across samples (Buckby, Cotton, Cosgrave, Killackey, & Yung, 2008; Burns & Eidelson, 1998; Kiernan, Laurent, Joiner, Catanzaro, & MacLachlan, 2001).

Dimensional Assessment: Laboratory Measures

In laboratory settings, a number of studies have examined affective responses to positively-valenced stimuli as a means of exploring the nature of anhedonic symptoms. These studies have suggested that individuals with depression generally rate positively-valenced stimuli as being less positive, less arousing, or less able to affect their mood as compared to controls (H. Berenbaum, 1992; H. Berenbaum, Oltmanns, T.F., 1992; Dunn, Dalgleish, Lawrence, Cusack, & Ogilvie, 2004; Rottenberg, Gross, & Gotlib, 2005; Rottenberg, Kasch, Gross, & Gotlib, 2002; Sigmon & Nelson-Gray, 1992; Sloan, Strauss, Quirk, & Sajatovic, 1997; Sloan, Strauss, & Wisner, 2001; Wexler, Levenson, Warrenburg, & Price, 1994) although a larger number of studies have reported no group differences in these ratings (Allen, Trinder, & Brennan, 1999; Dichter, Tomarken, Shelton, & Sutton, 2004; Forbes & Dahl, 2005; Gehricke & Shapiro, 2000; Kaviani, et al., 2004; Keedwell, et al., 2005a; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005b; Mitterschiffthaler, et al., 2003; Renneberg, Heyn, Gebhard, & Bachmann, 2005; Surguladze, et al., 2005; Tremeau, et al., 2005; Tsai, Pole, Levenson, & Munoz, 2003).

A potential caveat to this approach is whether reductions in affective responsiveness to positively-valenced stimuli are specific to experienced pleasure. One alternative explanation is that individuals with depression simply show a global flattening that encompasses both positive and negative emotions. Supporting the affective-flattening hypothesis, a recent meta-analysis of studies that measured physiologic or subjective affective responses found that

depression was associated with blunted reactivity to both positively- and negatively-valenced stimuli (Bylsma, Morris, & Rottenberg, 2008). Although it is notable that in the Bylsma analysis the effect size for positive stimuli is roughly double that for negative stimuli, their results suggest that at least part of the decline in hedonic responses may be due to a generalized affective blunting, rather than a specific deficit in experienced pleasure.

The “sweet taste test” provides another approach to assessing hedonic capacity. As part of the sweet taste test, participants rate the pleasantness of different sucrose concentrations. An advantage of this test is that it closely mirrors animal measures of hedonic experience. It is therefore of particular interest hat across four separate studies using the sweet taste test, individuals with depression and matched controls have shown no differences in reported hedonic impact (Amsterdam, Settle, Doty, Abelman, & Winokur, 1987; Berlin, 1998; Dichter, Smoski, Kampov-Polevoy, Gallop, & Garbutt; Kazes, et al., 1994). On the surface this suggests that there is no deficit in hedonic capacity to experience a natural reinforcer in MDD. A concern may be raised, however, as there are substantial individual differences in taste sensitivity (Duffy & Bartoshuk, 2000) that may make such measures insensitive to state changes in hedonic perceptions. In summary, the literature suggests reductions in hedonic capacity in MDD, although the generalizability of such deficits remains unclear.

Additional laboratory studies have used reinforcement paradigms to explore anhedonia in depression. One well-replicated finding has been that individuals with depression fail to develop a response bias towards rewarded

stimuli (Henriques, Glowacki, & Davidson, 1994; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Pizzagalli, Jahn, & O'Shea, 2005). These paradigms use discrimination tasks in which subjects must categorize a briefly presented stimulus as belonging to category A or B. Importantly, these paradigms use a pay-off matrix so that subjects are more rewarded for correctly guessing category A, as opposed to category B, with no punishment associated with incorrect guesses. Healthy control subjects typically develop a response bias toward the more rewarding option, whereas MDD patients do not. These elegant studies provide strong evidence for an insensitivity to reward-relevant information in MDD. One limitation, however, is whether these reinforcement deficits are driven by reduced hedonic capacity, diminished motivation, or both.

Finally, several recent studies compared ratings of experienced emotion in individuals with current depression, remitted depression and never depressed controls across conditions that involved anticipating and experiencing rewards and punishments (McFarland & Klein, 2009). Participants rated their emotions across ten dimensions in response to four experimental conditions: anticipating monetary rewards, anticipating an unpleasant sensory stimulus (cold press), no change, and avoiding an unpleasant sensory stimulus. No differences between the three groups were reported for anticipating unpleasant stimuli, no change, or the avoidance of an unpleasant stimulus. In contrast, during reward anticipation, individuals with current MDD showed significantly reduced ratings of positive emotions as compared to controls, and slightly reduced ratings compared to individuals with prior depression. Although this study did not test motivation *per*

se, these data provide novel evidence of a deficit in experienced emotion during reward anticipation in MDD.

Reconciling Laboratory and Self-Report Measures of Anhedonia

In comparing clinical, self-report and laboratory measures of anhedonia, it is puzzling that self-report measures of anhedonia, which primarily emphasize pleasure and positive emotionality, should differ from laboratory measures of affective responses to positive stimuli. One possibility is that these different classes of measures do not actually assess the same construct. Self-report measures may be broadly divided into two groups, depending on whether they are asking an individual to report on current emotions (as is common during laboratory tasks), or non-current emotions (as is common for trait and clinical-symptom inventories) (Robinson & Clore, 2002b). Importantly, these different types of measures may rely on distinct types of cognitive processing; reports of current emotions assess primarily interoceptive ability to report on momentary affective experience, whereas non-current inventories may require either episodic memory retrieval in cases of common symptom inventories, or affective forecasting in response to hypothetical scenarios, as is the case with some trait measures. The former is subject to retrospective bias, while the latter requires patients to engage in affective forecasting regarding hypothetical future scenarios (e.g., “how much would you enjoy a walk in park on a sunny day?”). In both cases, measures of recent symptoms and/or prediction of enjoyment in hypothetical scenarios may be only modestly related to laboratory measures of

in-the-moment-experience (Robinson & Clore, 2002a), especially in patient populations (Strauss & Gold, 2012). Consistent with these concerns, recent studies employing ecological-moment-assessment (EMA) techniques have observed only moderate relationships between EMA reports and trait-inventories, especially in patient populations (Solhan, Trull, Jahng, & Wood, 2009). These results suggest that despite the high test-retest reliability of trait and clinical instruments, they may possess relatively modest predictive validity for momentary affective experience in the laboratory.

Assessment of Anhedonia: More than a feeling?

If laboratory-based ratings of positive stimuli and symptom inventories do not assess different constructs, which is most clinically relevant? One way to address this question is to operationalize anhedonia as a behavioral pattern characterized by withdrawal and isolation, rather than an affective state. From this perspective, anhedonia is the end-result of debilitating cycle in which individuals predict that they will not enjoy things that they used to enjoy, and on the basis of this prediction, cease to engage in them. As a direct consequence of this behavioral withdrawal, the individual begins to notice that their life is increasingly devoid of things they enjoy, and (erroneously) conclude that this is because they no longer have the capacity to enjoy things. This formulation views anhedonia as a primarily behavioral symptom, and may require behavioral measures that are sensitive to motivation.

Taken together, the reviewed evidence suggests that while diagnosis of anhedonia assesses both motivation and experience of pleasure, current questionnaire and laboratory measures of anhedonia have largely emphasized the latter; there are few laboratory studies that have directly assessed motivation in MDD. In laboratory settings, a number of studies have found evidence for diminished responsiveness to positively-valenced stimuli, but the work of Bylsma et al., suggests that this may reflect a general affective flattening. Moreover, it remains unclear how closely related measures of affective responses to positively-valenced stimuli are to the construct of hedonic capacity. Importantly, the lack of group differences on the sweet-taste test raise potential doubts as to whether or not depression is associated with a specific deficit in the capacity to feel pleasure, at least at the level of basic sensory experience.

CHAPTER III

NEUROBIOLOGICAL MECHANISMS OF ANHEDONIA

In contrast to clinical studies of anhedonia, which have attended primarily to hedonic aspects of reward processing, preclinical research has focused heavily on sub-components such as reward motivation, learning, anticipation, hedonic response and satiety. These various aspects of reward have been linked to a variety of brain regions, neural circuits and neurotransmitters. These include the neurotransmitter dopamine and opioid neuropeptides, sub-cortical structures such as the basal ganglia and striatum (particularly the nucleus accumbens (NAcc), ventral pallidum (VP), ventral tegmental area (VTA), substantia nigra (SN), amygdala and hippocampus, as well as cortical regions such as the ventromedial prefrontal cortex (vmPFC), encompassing aspects of orbital frontal cortex (OFC), anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC). In this section I review the neural mechanisms that underlie motivational aspects of reward processing as well as evidence to support the role of this neurocircuitry in the pathophysiology of MDD.

Motivation and the Mesocorticolimbic DA system

Located within the pars compacta of the substantia nigra (SNpc) and VTA, DA neurons give rise to three ascending pathways: the nigrostriatal, mesolimbic and mesocortical pathways, as depicted in figure 1. The nigrostriatal pathway terminating in the dorsal caudate and putamen is heavily implicated in motor

control, and habit learning. The mesolimbic pathway terminates in the ventral striatum (including the NAcc), the amygdala and hippocampus, and is most closely associated with associative learning, reward motivation and reinforcement. The mesocortical pathway projects to cortical regions, including dense innervation of the ACC, with additional terminals in orbital frontal cortex, medial prefrontal cortex and the insula. This third pathway is strongly associated with working memory, attention, and inhibitory control.

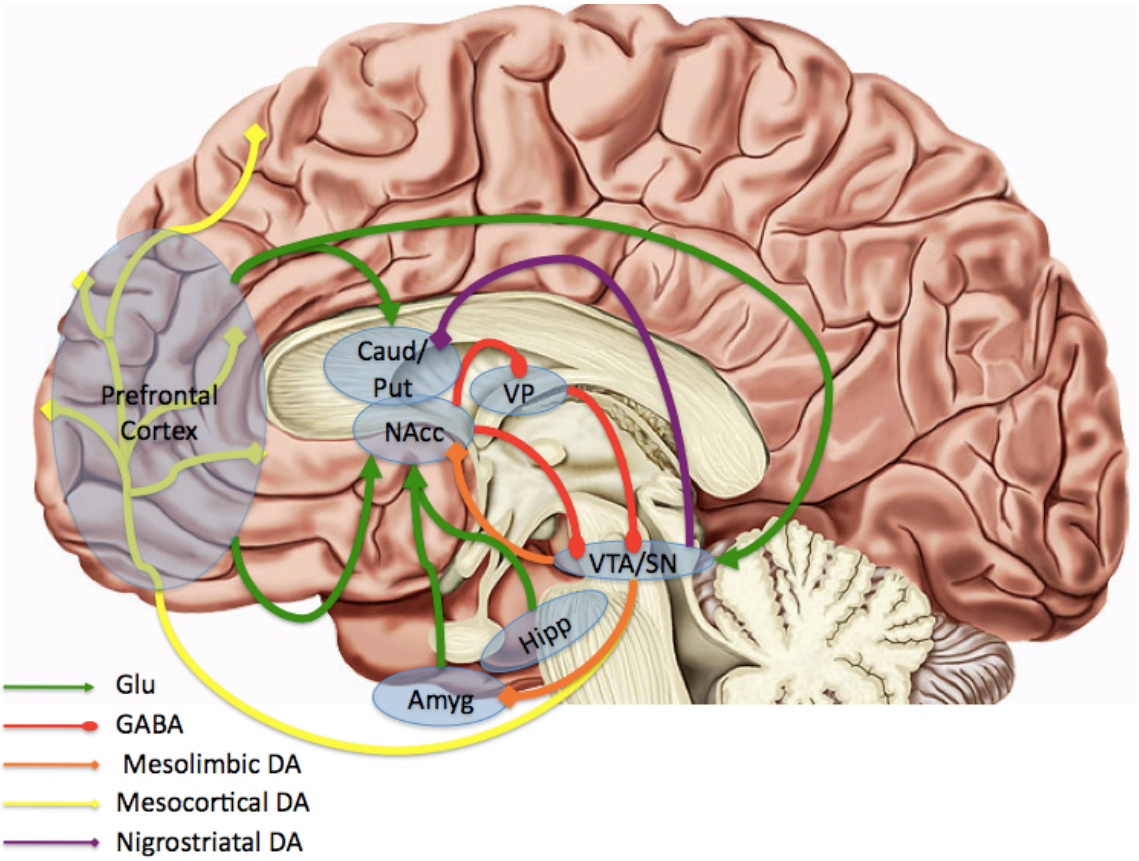

Figure 1: Schematic illustration of dopamine projection pathways and circuitry regulating DA release in the human brain. DA firing rates are maintained at tonic levels in part due to steady-state inhibitory firing from the ventral pallidum. Excitatory projections from prefrontal cortex project, amygdala and hippocampus synapse on striatal targets, including the nucleus accumbens. The nucleus accumbens sends GABAergic projections to the ventral pallidum, suppressing VP inhibition of VTA, thereby facilitating phasic burst-firing of VTA DA neurons. Note: Placement of structure labels is approximate. Amyg = amygdala; Caud = Caudate; DA = Dopamine; GABA = GABAergic projections; Glu = glutamatergic projections; Hipp = hippocampus; NAcc = nucleus accumbens; Put = Putamen; SN = substantia nigra; VP = ventral pallidum; VTA = ventral tegmental area

Midbrain DA neurons exhibit two distinct modes of firing, referred to as "tonic" and "phasic" (Grace & Bunney, 1984). Tonic DA activity refers to steady-state firing generated by intrinsic pacemaker-like characteristics of DA neurons. Phasic activity—also known as "burst firing"—involves a rapid series of action potentials that induce a rapid rise in extracellular DA at terminal projection targets. As additionally outlined in figure 1, initiation of phasic activity requires excitatory signals from a variety of areas, including the prefrontal cortex, pedunculpontinetegmentum (PPt) and subthalamic nucleus (Floresco, West, Ash, Moore, & Grace, 2003; Futami, Takakusaki, & Kitai, 1995) (Smith & Grace, 1992) as well as suppression of steady-state inhibitory signals arising from the NAcc and ventral pallidum (VP) (Sesack & Grace).

A key function of DA is to modulate the sensitivity of post-synaptic neurons to other types of input. In the striatum—the largest recipient of DA projections—DA may modulate the sensitivity of medium spiny neurons (MSN) to excitatory glutamatergic projections from prefrontal and limbic regions. As shown in figure 2, DA acts primarily on one of 5 post-synaptic G-protein coupled receptors, labeled D1-D5 (Cooper, 2003). These receptors are grouped into two "families", described as D1-like (including D1 and D5 receptors) and D2-like (D2, D3 and D4 receptors). Upon receptor stimulation, Both D1-like and D2-like receptors interact with adenylate cyclase (AC) (Surmeier, Ding, Day, Wang, & Shen, 2007). D1-like receptor stimulation increases AC activity through coupling with either G alpha S or ($G_{\alpha\text{-s})}$ G alpha olfactory ($G_{\alpha\text{-olf}}$), which results in

increased activation of protein kinase A (PKA) and subsequent phosphorylation of various intracellular targets. Recent evidence suggests that this intracellular pathway can result in increased responsiveness of MSNs to sustained release of glutamate, generating “up-states” (Surmeier, et al., 2007). In contrast, D2-like

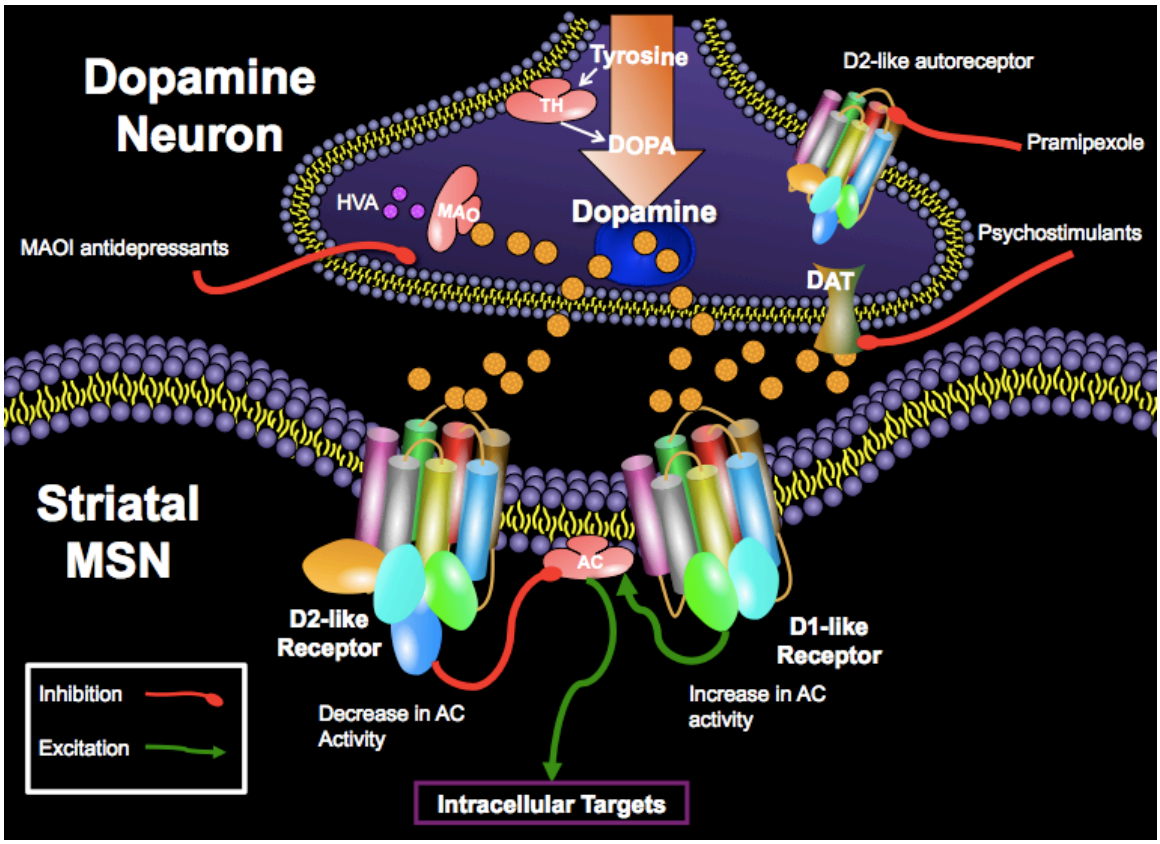

Figure 2: Schematic illustration of dopamine synapse on striatal medium spiny neuron. DA stimulation of D1-like receptors increases the activity of adenylate cyclase, while stimulation of D2-like receptors suppresses adenylate cyclase activity. DA may be removed from the synapse either by reuptake via the DA transporter or degradation by monoamine oxidase, resulting in the DA metabolite of homovanillic acid. Psychostimulants increase synaptic DA by blocking DAT function, while monoamine oxidase inhibitors block MAO activity and pramipexole inhibits DA autoreceptors. AC = adenylate cyclase; DAT = DA transporter; DOPA = 3,4-dihydroxyphenylalanine; HVA = homovanillic acid; MAO = monoamine oxidase; MAOI = monoamine oxidase inhibitor; MSN = medium spiny neuron; TH = tyrosine hydroxylase.

receptor binding results in decreased AC activity, thereby reducing the responsiveness of MSNs (“down states”) (Hernandez-Lopez, et al., 2000). Of note, due to their higher affinity for DA as well as their more centralized location on the post-synaptic membrane, D2-like receptors are often stimulated by tonic levels of DA release, whereas D1-like receptors are stimulated primarily during phasic DA release (Goto, Otani, & Grace, 2007).

Initial evidence for the role of DA in mediating motivation for rewards comes from the fact that 6-OHDA lesions of NAcc DA synapses do not impair hedonic liking expressions in rats (Berridge & Robinson, 1998). Similar effects have been found following the systemic administration of neuroleptic drugs—acting primarily on DAergic sites— which also failed to alter liking responses (Kaczmarek & Kiefer, 2000; Parker & Leeb, 1994; Pecina, Berridge, & Parker, 1997). Finally, DA burst-firing—which commonly occurs in response to unexpected rewards—ceases after the previously unexpected reward becomes predicted, despite the fact that the hedonic value of the predicted reward is presumably intact (Berridge, 2007; Schultz, 2006; Schultz, Dayan, & Montague, 1997). Even more striking evidence comes from studies using mice that have been genetically engineered to be incapable of endogenous DA synthesis without the aid of daily L-DOPA administration (Zhou & Palmiter, 1995). Suspension of these L-DOPA administrations for a single day can result in the near-total depletion of DA in the brain. However, even these highly DA-depleted mice still favor sucrose-water over regular water, and demonstrated a morphine-induced conditioned place-preference (Cannon & Palmiter, 2003; Hnasko, Sotak,

& Palmiter, 2005). Finally, studies have found that *increasing* DA shows no effect on liking behavior. Genetically modified mice that exhibit a knockdown of the Dopamine Transporter (DAT) gene, thereby resulting in increased extracellular DA, showed no alterations in liking responses (Pecina, et al., 1997). In sum, these findings provide clear evidence that DA function is neither necessary nor sufficient for hedonic liking responses to occur.

A second line of work has sought to demonstrate a pivotal role for DA in the motivation to pursue rewards, as indexed by overcoming response costs (Salamone, et al., 2007). As shown in figure 3, Salamone and colleagues developed experimental paradigms that evaluate an animal's willingness to work for a given reward. These paradigms, described herein as "effort-based decision-making" paradigms, include concurrent-choice tasks and progressive ratio tasks (Assadi, Yucel, & Pantelis, 2009). Initial studies employed a T-maze design, in which rats enter a T-shaped maze and made a choice between one arm of the maze containing a readily available food reward (Low-Cost/Low Reward, "LC/LR"), and another arm containing a larger food reward that was available only after climbing a barrier (High-Cost/High-Reward, "HC/HR"). Using this choice-paradigm, it was demonstrated that while control rats prefer the HC/HR option, rats with NAcc DA lesions or blockade of striatal D2 receptors show increased preference for the LC/LR option (Correa, Carlson, Wisniecki, & Salamone, 2002; Cousins, Atherton, Turner, & Salamone, 1996; Cousins & Salamone, 1994; Denk, et al., 2005; Salamone, et al., 2007).

Convergent evidence was found during an operant response concurrent-choice task, where rats must choose between eating freely-available, unpalatable "lab chow" (LC/LR option) or pressing a lever several times in order to receive a preferred food reward (HC/HR option). As with the T-maze paradigm, blockade of NAcc DA through either lesions of DA projection terminals with 6-OHDA will result in a reduced preference for the HR choice (Aberman & Salamone, 1999; Correa, et al., 2002; Cousins & Salamone, 1996; Hamill, Trevitt, Nowend, Carlson, & Salamone, 1999; Salamone, Correa, Mingote, & Weber, 2005; Salamone, et al., 1991). Additional studies have found that global blockade of DA using selective D1 or D2 receptor antagonists may also impair effort-based decision-making (Bardgett, Depenbrock, Downs, Points, & Green, 2009; Walton, et al., 2009), though selective impairment of phasic DA release does not (Zweifel, et al., 2009).

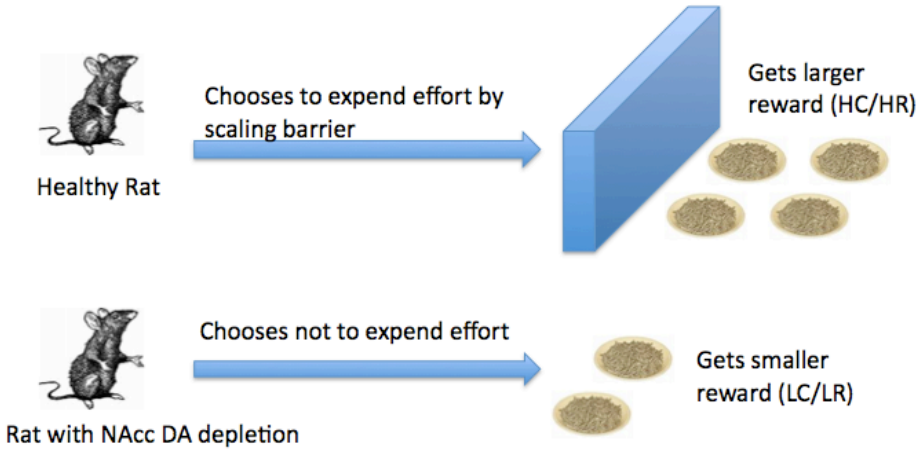

Figure 3: Schematic diagram of effort-based decision-making paradigms. Animals may choose between a smaller food reward that is readily available (LC/LR option) or a greater food reward that can only be obtained after climbing over a barrier (HC/HR option). Control rats choose the HC/HR option approximately 90% of the time, while DA depleted rats show a strong preference for the LC/LR option.

A key aspect of these paradigms for translational psychopathology research is the fact that control animals choose HC/HR options approximately 90% of the time, thereby suggesting that experimentally-induced increases in LC/LR choices can reasonably be interpreted as pathological in nature, rather than a minor shift in normative preferences. In addition, multiple control experiments have been performed to rule out possible confounding factors, such as alterations in the ability to engage in voluntary movement, or diminished understanding of reward contingencies. For example, in conditions where reward is removed entirely from the LC/LR option, or the paradigm is modified so that both LC/LR and HC/HR options require equal effort, NAcc DA depleted rats cease to differ from control animals (Denk, et al., 2005; Salamone, 1996). Additionally, one recent study confirmed that NAcc DA influences effort-expenditure preferences even when controlling for differences in reward delay, as HC/HR options often require extra time to complete (Floresco, St Onge, Ghods-Sharifi, & Winstanley, 2008). These additional studies suggest that experimentally-induced preferences for LC/LR options are; 1) sufficiently abnormal to be construed as a pathological deficit in motivation, and 2) do not result from impaired understanding of choice contingencies, physical inability, or temporal delay. Taken together, these findings provide strong evidence for the role in DA as encoding the motivational aspects of reward processing, while being relatively uninvolved in the hedonic experience.

Evidence for DA Dysfunction in Depression

Given the robust associations between DA and reward motivation, it would be predicted that if motivational deficits are indeed an important feature of MDD, evidence for DAergic dysfunction should be detectable in patient samples. As with other neurotransmitters and biological systems, however, definitive support for DA dysfunction in MDD remains elusive. One challenge to uncovering the role of DA in MDD is that many studies have employed group designs with heterogeneous samples that are not limited to patients with anhedonic symptoms, much less specific motivational and consummatory subtypes. Such heterogeneity may mask group differences in DA function, as well as specific within-group associations between DA and anhedonia. This problem is worsened by the fact that assessment instruments for anhedonia are heavily weighted towards pleasure responses, which are unlikely to be strongly associated with DA function. Nevertheless, multiple studies support the hypothesis that abnormalities in DA are indeed common in patients with MDD, if not necessarily ubiquitous across all clinical presentations.

Initial data supporting a role of DA in MDD comes from studies of DA turnover, which observed that individuals with MDD have decreased cerebrospinal fluid (CSF) levels of homovanillic acid (HVA), the primary metabolite of DA (Berger, et al., 1980; Lambert, Johansson, Agren, & Friberg, 2000; van Praag, Korf, & Schut, 1973; Willner, 1983a). These studies suggest the presence of lowered basal DAergic tone in MDD. Additionally, pharmacological interventions that block or deplete DA can induce or deepen

depressive symptoms in currently depressed or remitted individuals (Bremner, et al., 2003; Hasler, et al., 2008; Ruhe, Mason, & Schene, 2007), further implicating DA dysfunction in MDD.

In animal models of depression, several lines of evidence also support the role of DA dysfunction. The Flinders sensitive line (FSL), a genetic animal model of MDD, exhibit reduced basal concentrations of DA in the NAcc and slower rates of DA release in the NAcc as compared to Sprague-Dawley (SD) rats (Zangen, Nakash, Overstreet, & Yadid, 2001). One contributing cause of reduced extracellular DA concentrations in DA neuron terminal regions is altered firing patterns of midbrain DA neurons themselves. Consistent with this explanation, FSL rats have been observed to exhibit marked impairment in phasic burst firing (Friedman, et al., 2007) (for a review, see (Yadid & Friedman, 2008)). Another animal model of depression that implicates DA function is the post-psychostimulant withdrawal model (Barr & Markou, 2005; Barr, Markou, & Phillips, 2002). This model is particularly relevant for research on DA in MDD, as it produces a significant number of symptoms associated with MDD (Markou, Kosten, & Koob, 1998) and results from direct manipulation of the DA system. Consistent with effort-expenditure deficits observed by Salamone and colleagues following NAcc DA blockade, psychostimulant withdrawal has been shown to reduce both NAcc extracellular DA levels (Weiss, Markou, Lorang, & Koob, 1992) and effort-expenditure for sucrose rewards during a progressive ratio task (Barr & Phillips, 1999).

DA acting drugs, particularly D2 agonists, have antidepressant properties

in animal models of depression (for a review see (Gershon, Vishne, & Grunhaus, 2007)). Indeed, a large number of studies have demonstrated that chronic administration of various classes of antidepressant medication show a common effect of increasing D2-like receptor binding or sensitivity in the NAcc, and increased psychomotor responses to psychostimulants (D'Aquila, Collu, Gessa, & Serra, 2000; Gershon, et al., 2007). Such effects are observed following chronic treatment with both tricyclic antidepressants and SSRIs, even though the acute effects of these agents are primarily mediated through serotonergic and noradrenergic mechanisms. Notably, however, the antidepressant effects of these agents can be blocked entirely by D2-like receptor antagonists. Finally, the selective serotonin-reuptake enhancer (SSRE) tianeptine has been shown to have robust antidepressant properties, a finding contrary to what would be expected if MDD were associated with a specific deficit in 5HT signaling (Kasper & McEwen, 2008). While the mechanisms that underlie the antidepressant properties of tianeptine are unclear, it is noteworthy that this compound has been shown to increase NAcc extracellular DA levels as well as DA turnover in rodents (Invernizzi, Pozzi, Garattini, & Samanin, 1992).

In humans, pharmacological enhancement of DA signaling provides at least temporary antidepressant effects, and has been seen with DA agonists such as bromocriptine, piribedil, ropinirole and pramipexole (Bouras & Bridges, 1982; Cassano, et al., 2005; Shopsin & Gershon, 1978; Sitland-Marken, Wells, Froemming, Chu, & Brown, 1990; Vale, Espejel, & Dominguez, 1971; Waehrens & Gerlach, 1981). DAT inhibitors nomifensine (Kapur & Mann, 1992),

methylphenidate (El-Mallakh, 2000), amineptine and bupropion also exhibit varying degrees of antidepressant effects, further highlighting the possible role DA in MDD (see section 5 for further review) (Kapur & Mann, 1992; Stahl, 2000).

Human neuroimaging studies of DA synthesis capacity have shown reduced L-DOPA uptake in MDD (Agren & Reibring, 1994). Moreover, studies exploring different sub-groups have found that L-DOPA alterations in the striatum are present in depressed individuals with flat affect or psychomotor slowing, but not depressed individuals without these symptoms (Bragulat, et al., 2007; Martinot, et al., 2001). Patients with reduced DA synthesis in Parkinson's disease also show increased rates of MDD (Koerts, Leenders, Koning, Portman, & van Beilen, 2007). These data suggest that reduced DA synthesis capacity may be linked to specific symptoms in MDD.

Additional evidence of altered DA function in MDD comes from Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) imaging of the DA transporter (DAT), where depression has been associated with both lower (Meyer, et al., 2001) and higher (Amsterdam & Newberg, 2007; Laasonen-Balk, et al., 1999; Yang, et al., 2008) DAT binding potential in the striatum. Of note, however, the one study that restricted its MDD patient sample to individuals with anhedonic symptoms reported decreased DAT binding (Sarchiapone, et al., 2006). Monoamine oxidase A, a metabolizing enzyme of DA and other monoamines has been shown to be elevated in MDD across multiple brain regions, suggesting one possible mechanism through which observed decreases in monoamine

transmission may occur during a depressive episode (Meyer, et al., 2006). Heightened activity of MAOA in MDD may partially explain the efficacy of MAO inhibitors, which likely lead to the increased availability of monoamines—including DA—by returning MAOA activity to normative levels.

Studies of DA receptor availability in MDD have to date produced mixed results. In some cases, increased striatal D2/D3 receptor binding has been shown to occur in heterogeneous depressed samples (D'Haenen H & Bossuyt, 1994; Shah, Ogilvie, Goodwin, & Ebmeier, 1997), as well as in patient samples with specific symptoms of psychomotor slowing (Meyer, et al., 2006). This increase in D2/D3 receptor availability would appear to contradict animal data in which antidepressant responses are associated with increased D2-like binding in the striatum. The source of this discrepancy is unclear, but it may be noted that the patients in human studies were not medication naïve. Other studies using medication-naïve or medication-free patients have failed to identify group differences in striatal receptor binding (Hirvonen, et al., 2008; Parsey, et al., 2001), while one additional small study showed variable changes in D2-like binding following treatment with SSRIs, with those showing increased binding showing more clinical improvement than those who did not (Klimke, et al., 1999). Taken together, these studies suggest a possible role of D2-like receptors in downstream effects of antidepressant treatment. However, the precise nature of the effect and how alterations in D2-like receptor availability may relate to DA function as a whole remains unclear. Moreover the use of heterogeneous samples, and limited exploration of specific symptoms, has precluded

examination of specific relationships between D2-like function and motivational anhedonia.

As for D1-like receptors, a recent study of D1 receptors using PET-[^{11}C]NNC-112 found reduced D1-like receptor binding in the striatum bilaterally in a sample of individuals with MDD (Cannon, et al., 2009). Anhedonia as assessed by a sub-scale of the IDS-C was not correlated with change in binding potential in the MDD group. However, as with other commonly used assessments of anhedonia, the anhedonia subscale from the IDS-C primarily emphasizes consummatory, rather than motivational aspects.

It is additionally worth noting that a proposed role for DA dysfunction in the pathophysiology of MDD is consistent with current etiological models that highlight interactions between genetic risk factors and stressful life events in the onset, maintenance and relapse of MDD (Caspi, et al., 2003; Hammen, 2005; Kendler, Karkowski, & Prescott, 1999; Kessler, 1997). Genetic studies have identified several polymorphisms related to DAergic function that increase risk for the development of depression. The most reliable of these findings is allelic variations in the DRD4 gene (Lopez Leon, et al., 2005) and D3 receptor gene in both unipolar and bipolar depression (Chiaroni, et al., 2000; Dikeos, et al., 1999). Additionally, the effects of chronic and acute stress are well known to have significant consequences on the DA system. Stress has been shown to increase glucocorticoid signaling (Holsboer, 2000), precipitate neuronal degeneration in the hippocampus (Sapolsky, 2000) and medial prefrontal cortex (McEwen, 2005; Radley, et al., 2006), decrease the availability of brain-derived neurotrophic

factor (BDNF) (Duman, 2009), and increase levels of pro-inflammatory cytokines in the brain (Dowlati, et al.; Maier & Watkins, 1998). Importantly, all of these modulations have direct influence on DA function. Glucocorticoids modulate firing of DA neurons (Piazza, Barrot, et al., 1996; Piazza, Rouge-Pont, et al., 1996), and regions that suffer glucocorticoid-mediated atrophy are key regulators of mesolimbic and mesocortical DA projection pathways (Arnsten, 2009; Lisman & Grace, 2005). BDNF has been shown to regulate VTA DA neurons (Conner, Lauterborn, Yan, Gall, & Varon, 1997), and alterations in BDNF can influence mesolimbic DA responses to reward and resiliency to stress (Berton, et al., 2006; Cordeira, Frank, Sena-Esteves, Pothos, & Rios). Finally, increases in pro-inflammatory cytokines can impact both the metabolism and synthesis of DA (Anisman, Merali, & Hayley, 2008) so as to result in reduced DA availability.

Taken together, the above studies provide evidence that 1) MDD is associated with compromised DA function, 2) manipulations of the DA system contribute to the actions of antidepressants and 3) alterations of DA function are often a downstream consequence of genetic and environmental risk factors, such as exposure to stress. These positive findings are qualified by the presence of null findings, as well as the difficulty in interpretation associated with some of the studies. Notably, some of the findings appear specific to sub-populations of depressed individuals defined by the presence or absence of specific symptoms. This observation is consistent with the central claim that rigorous phenotypic description—such as distinct measures for motivational and consummatory aspects of reward— is crucial for reliable results with biological measures.

CHAPTER IV

DEVELOPING A TRANSLATIONAL MODEL OF REWARD MOTIVATION

To address the clear need to develop a laboratory-based measure in humans that could be used to assess motivational aspects of reward processing, I developed the Effort-Expenditure for Rewards Task (EEfRT or "effort"). The EEfRT paradigm is based on a concurrent choice paradigm devised by Salamone and colleagues to explore effort-based decision-making in rodents[198]. In designing this task, there were several considerations that were paramount. First and foremost, the goal of the task was to serve as a translational adaptation of preclinical effort-based decision-making tasks that could be used to enhance the relevance of these preclinical models to clinical research as well as to facilitate "back-translation" of findings from human studies toward the generation o novel experiments in animals. This "back-translatability" was viewed as being especially crucial, as it is critical aspect of animal model validation that is often neglected (Fernando & Robbins, 2012). Second, it was vital that the EEfRT was able to accurately assess individual differences in *motivation* to work for rewards, and not differences in actual or perceived ability to perform the work. For instance, early design ideas included asking participants to go up and down several flights of stairs in order to gain rewards, but there was concern that genuine differences in physical fitness would confound inferences about subject motivation. Similarly, cognitive effort challenges, such as arithmetic problems or

puzzles, which have been used in past studies (Shechter, Durik, Miyamoto, & Harackiewicz, 2011), can produce anxiety in subjects about their ability to perform the task, which can influence decision-making. Consequently, the effort requirements of the EEfRT focused on speeded manual presses in the form of button pressing, a form of effort that has been previously used to probe motivational systems in humans (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001).

Given these considerations, the EEfRT was designed as a multi-trial game in which participants are given an opportunity on each trial to choose between two different task difficulty levels in order to obtain monetary rewards (Figure 4). For all trials, participants make repeated manual button presses within a short period of time. Each button press raises the level of a virtual "bar" viewed onscreen by the participant. Participants are eligible to win the money allotted for each trial if they raise the bar to the "top" within the prescribed time period. Each trial presents the subject with a choice between two levels of task difficulty, a 'hard task' (HC/HR option) and an 'easy task' (LC/LR option). Successful completion of hard-task trials requires the subject to make 100 button presses, using the non-dominant little finger within 21 seconds, while successful completion of easy-task trials requires the subject to make 30 button presses, using the dominant index finger within 7 seconds. For easy-task trials, subjects are eligible to win the same amount, $1.00, on each trial if they successfully completed the task. For hard-task choices, subjects are eligible to win higher amounts that vary per trial within a range of $1.24 – $4.30 ("reward magnitude").

Subjects are not guaranteed to win the reward if they completed the task for a given trial; some trials are “win” trials, in which the subject received the stated reward amount, while others are “no win” trials, in which the subject receives no money for completing the chosen task. To help subjects determine which trials are more likely to be win trials, subjects are provided with accurate probability cues at the beginning of each trial. Trials have three levels of probability: “high” 88% probability of being a win trial, “medium” 50% and “low” 12%. Probability levels apply to both the hard task and the easy task, and there were equal proportions of each probability level across the experiment. Each level of probability appears once in conjunction with each level of reward value for the hard task. All subjects receive trials presented in the same randomized order.

We note that the inclusion of a probability manipulation represents a departure from preclinical paradigms, which have focused on effort-expenditure alone (Cousins & Salamone, 1994; Walton, Bannerman, & Rushworth, 2002). There were several reasons why this manipulation was the included. The first was to improve the ecological validity of the EEfRT; positive events are rarely if ever guaranteed, and unanticipated setbacks can scuttle the pursuit of even mundane rewards in MDD patients. Second, preclinical data suggest that processing of probability information during cost/benefit decision-making is similarly dependent of mesolimbic DA function. Paralleling findings with effort, DA antagonism reduces tolerance for probability costs, shifting preference away from larger, uncertain rewards to guaranteed smaller rewards, while amphetamine

increases preference for larger, riskier rewards (St. Onge, Chiu, & Floresco, 2010; St. Onge & Floresco, 2008) but see also (Zeeb, Robbins, & Winstanley, 2009). These findings are consistent with theoretical models suggesting that mesolimbic DA encodes different types of response costs (e.g., effort and probability) in a similar manner (Phillips, Walton, & Jhou, 2007). Finally, the inclusion of probability, which effectively discounted the reward magnitude of the HC/HR option, helped to improve the sensitivity of the task for detecting individual differences.

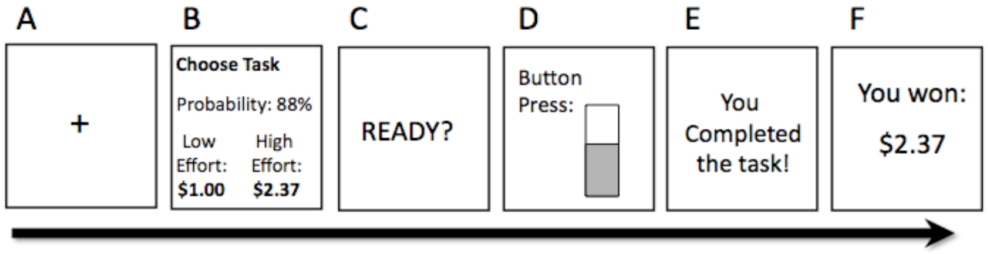

Figure 4: Schematic diagram of a single trial of the EEfRT. **A.** Trials begin with a 1s fixation cue. **B.** Subjects are then presented with a 5s choice period where they are given information regarding the reward magnitude of the High Effort option, and the probability of receiving a reward. **C.** 1s "ready" screen. **D.** Subjects make rapid button presses to complete the chosen task and watch a virtual "bar" on the screen that fills up as they progress to their completion goal. **E.** Subjects receive feedback on whether they completed the task. **F.** Subjects receive feedback as to whether they received any money for that trial.

All trials of the EEfRT begin with a 1-second fixation cross, following a 5-second choice period in which subjects are presented with information regarding the probability of receiving reward and the reward magnitude of the hard task. Subjects are told that if they do not make a choice within 5 seconds, they would be randomly assigned to either the easy or the hard task for that trial. After making a choice, subjects are then shown a 1-second "Ready" screen and then prompted to complete the task. Following task completion, subjects are shown a

2 second feedback screen informing them that the task was successfully or unsuccessfully completed. If subjects successfully completed the task, then a second feedback screen appears for 2 seconds in which subjects were told whether they won money for that trial (reward feedback). In total, easy-task trials take approximately 15 seconds, whereas hard-task trials take approximately 30 seconds.

Subjects are told that they will receive a base-rate of compensation for their participation in the form of either money or course-credit. In addition, they are told that two of their win trials would be randomly selected at the end of the experiment as “incentive trials,” for which they would receive the actual amount won on those trials. Subjects are informed that they have twenty minutes to play as many trials as they can Since hard-task trials take approximately twice as much time to complete as easy-task trials, the number of trials that a subject is able to play depends in part on the choices that he or she makes. This means that making more hard-task trials toward the beginning of the experiment could reduce the total number of trials, which could in turn mean that a subject did not get a chance to play high-value, high-probability trials that might have appeared towards the end of the playing time. This trade-off is explained clearly to the subject. Importantly, subjects are not provided with any information regarding the distribution of trial types. The goal of this trade-off is to ensure that neither a strategy of always choosing the easy or the hard option could lead to an ‘optimal’ performance on the task. Finally, the complexity of variables (varying monetary reward levels, probability), do not lend itself to a formal calculation of an optimal

response selection, and subjects are required to make decisions within a brief amount of time. This was done to help ensure that subject decisions reflected individual differences in the willingness to expend effort for a given level of expected reward value. The EEfRT was programmed in Matlab (Matlab for Windows, Rel. 2007b. Mathworks Inc., Natick, MA) using the Psychtoolbox version 2.0.

Methods

Participants

61 participants (64% female) were recruited through Vanderbilt University and the community to participate in this study. Subjects were chosen from a larger sample of 324 undergraduates who were pre-screened using a brief self-report measure of hedonic responsiveness, the Snaith-Hamilton Pleasure Scale (SHAPS) [58]. This measure was used to ensure an appropriate range of trait anhedonia scores in our experimental sample.

Study Procedure

Upon arriving to the lab, participants first reviewed a consent form and provided written consent. Participants were then asked to complete all self-report measures. After this, participants were provided with a series of task instructions. After participants read through the instructions, they were asked several simple questions to ensure they understood the task and its contingencies. Participants then played four practice trials. For the first two trials, the participant was

instructed to choose the easy and hard task respectively, in order to gain familiarity with the level of effort required for each task. For the last two practice trials, the subject was free to choose. After completion of practice trials, the participant was asked if he or she had any questions. If not, then the subject commenced playing for a timed period of 20 minutes.

Measures

In addition to the EEfRT, several self-report measures of state and trait anhedonia were collected. The Chapman physical and social anhedonia scales (Chapman, et al., 1976) served as the primary trait measure for anhedonia.

Data Reduction and Analysis

Because subjects could only play for 20 minutes, the number of trials completed during that time varied from subject to subject (Mean trials completed = 54, SD = 4.74, Range = 47-69 trials). For consistency of analysis, only the first 50 trials were used. Data were exported from Matlab into SPSS (SPSS for Macintosh, Rel. 16.0. 2008. Chicago: SPSS Inc.) for further analysis.

Statistical Analysis

Data were analyzed using two statistical approaches. The first approach used repeated measures ANOVA and correlations. For these analyses, mean proportions of hard-task choices were created for all subjects across each level of probability. Proportions of hard-task choices and responses to self-report

questionnaires were approximately normally distributed, and therefore parametric tests were used for inferential statistics.

The second approach used generalized estimating equations (GEE). GEE is a generalized regression model that is used to investigate continuous or logistic outcome variables in which the residuals are correlated (Zeger & Liang, 1986). The term “Generalized” in this context means that different distributions (e.g. normal, dichotomous, Poisson) can be modeled through a link function. Importantly, GEE models allow for trial-by-trial modeling of both time-varying parameters (e.g., changes in reward value of the hard-task for each trial) as well as fixed effects (e.g., scores on anhedonia measures). The dependent measure was the dichotomous outcome of hard or easy task choice, and we used a binary logistic distribution to model the probability of choosing the hard-task. For all models, independent variables included probability, reward, expected value (reward magnitude X probability), trait anhedonia (Chapman) and gender. Separate models assessed the effects of trait anhedonia, and the interaction between trait anhedonia with probability level, reward magnitude and/or expected value.

Effects of Fatigue During the EEfRT

An important requirement for the EEfRT is that it measure individual differences in motivation for rewards, rather than individual differences in ability or fatigue. The task was specifically designed to require a meaningful difference in effort between hard and easy-task choices while still being simple enough to

ensure that all subjects were capable of completing either task, and that subjects would not reach a point of exhaustion. Two manipulation checks were used to ensure that neither ability nor fatigue shaped our results. First, we examined the completion rate across all trials for each subject, and found that all subjects completed between 96%-100% of trials. This suggests that all subjects were readily able to complete both the hard and easy tasks throughout the experiment. As a second manipulation check, we used trial number as an additional covariate in each of our GEE models.

Results

Main Effects of the EFFRT

Across the sample, subjects displayed significant variability in their willingness to expend effort for rewards, with proportion of HC/HR options ranging from a low of 16% to 75% of total choices (Figure 5). A Repeated Measures ANOVA found a significant main effect for probability level on the proportion of hard task choices, with higher probability trials levels associated with more hard-task choices ($f_{(2,120)} = 139.8$, $p < 0.001$). Across all subjects, proportion of hard-task choices for medium probability trials were moderately correlated with proportion of hard-task choices for both high probability ($r = 0.31$, $p < 0.05$) and low probability trials ($r = 0.31$, $p < 0.05$). High probability and low probability trials were uncorrelated ($r = -0.02$, p = ns). We also found a main effect of gender, with men making more hard-task choices than women ($f_{(1,59)}$ =

3.9, p = 0.05). Consequently, gender was included as a covariate in all subsequent analyses.

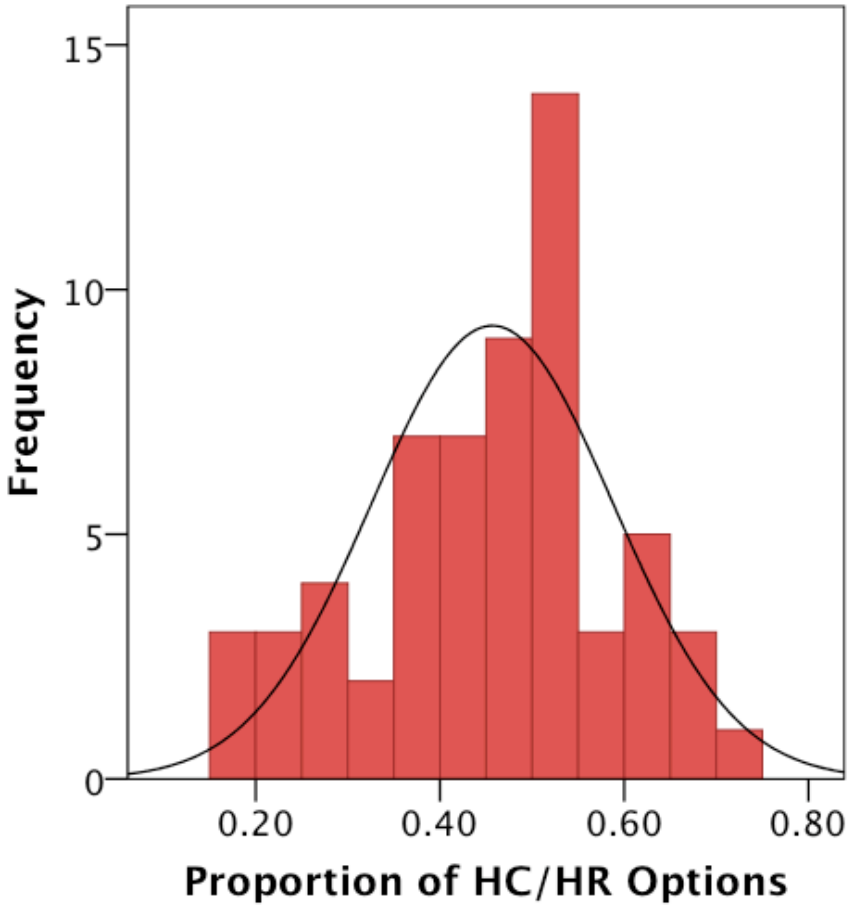

Figure 5: Distribution of the proportion of HC/HR options made by a sample of healthy volunteers, indicating significant variability in the willingness to expend effort for rewards.

Effects of Trait Anhedonia on EEfRT Performance

Partial correlations (controlling for gender) between proportion of HC/HR options and self-report measures demonstrated a modest association between willingness to expend effort across all trial and self-reported trait anhedonia (r = -0.30, p <0.05) (Figure 6).

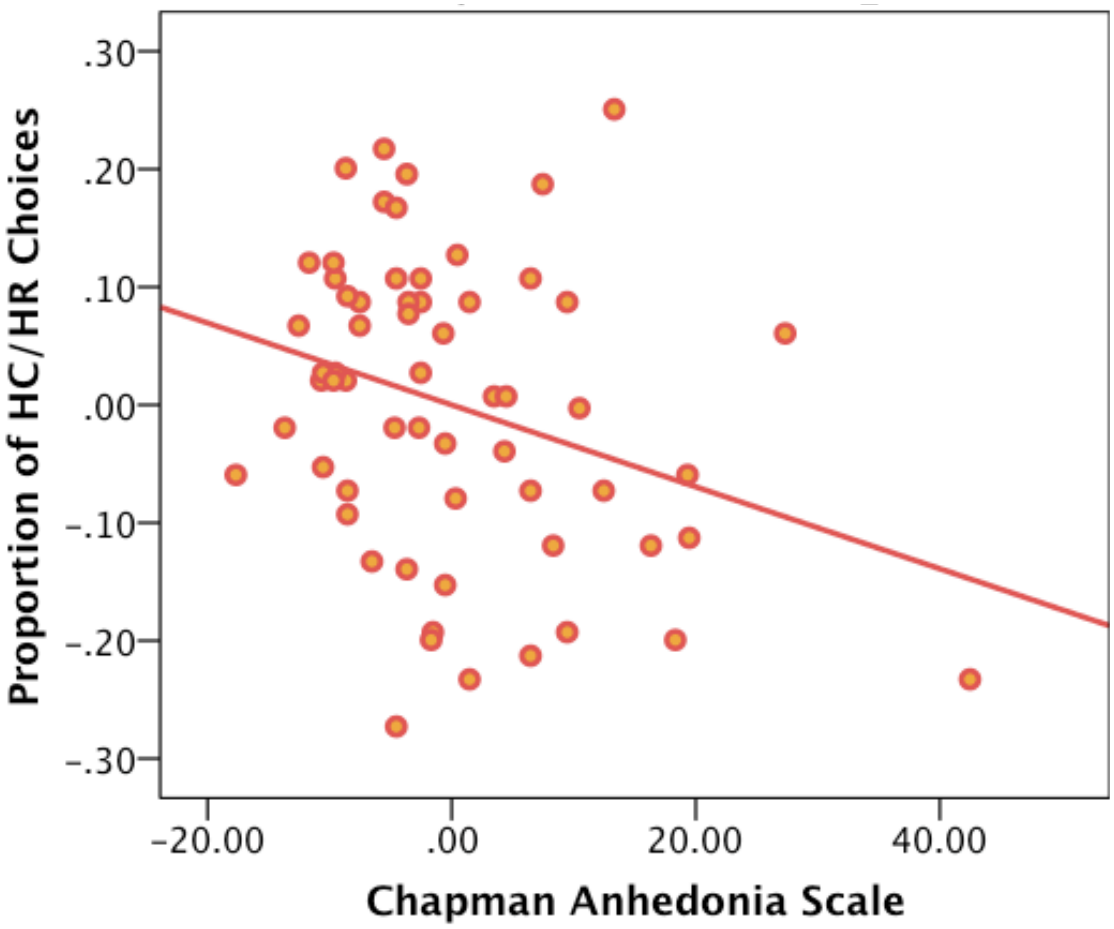

Figure 6: Association between the Chapman Anhedonia Scales and overall proportion of HC/HR choices during the EEfRT. *r* = -0.30, *p* < 0.05.

To further characterize the association between Chapman Anhedonia scores and EEfRT performance, we tested a single GEE model that included the Chapman scores, trial probability level, hard-task reward value, expected value

(EV), trial number and gender as covariates. All reward parameters (probability, reward magnitude and EV) were significant predictors of choice behavior (p's < 0.05) as was trial number (b = -0.008, p < .05), indicating some fatigue over the course of the task. This model also revealed a significant effect of Chapman Anhedonia scale, even when controlling for trial-wise variables throughout the task (*b* = -0.02, *p* <0.05).

Discussion

The present study had two goals: 1) to validate the EEfRT as a novel effort-based decision-making task that could serve as an objective measure of individual differences in reward motivation; and 2) to explore the utility of the EEfRT in predicting trait anhedonia. In accordance with our first hypothesis, we found that individuals showed substantial variability in their willingness to expend greater effort for differing levels of reward magnitude and probability. This is consistent with well-validated self-report questionnaires, which also suggest significant variability in reported levels of motivation for various types of rewards (Costa & McCrae, 1992; Duckworth, Peterson, Matthews, & Kelly, 2007; Duckworth & Quinn, 2009; Duckworth, Quinn, Lynam, Loeber, & Stouthamer-Loeber, 2011).

For the second aim, we found a significant main effect of trait anhedonia on EEfRT performance, such that individuals with higher levels of reported-trait anhedonia chose fewer HC/HR options. However, the effect size of this relationship was relatively modest. While this association provides some

preliminary validation of the task, an important limitation of this analysis is that the Chapman Anhedonia Scales assesses a subject's beliefs about whether she generally enjoys various experiences. As discussed in chapters II and III, there is growing evidence from both clinical and preclinical studies to suggest that motivational and hedonic responsiveness rely on separable neural systems, and may therefore not necessarily be expected to show strong linear associations.

We also found a main effect of gender across all analyses, with women consistently making fewer hard-task choices than men. Given that the EEfRT is a computer-based task that emphasizes physical performance, it is conceivable that the task is gender-biased. Additional studies will determine whether these observed differences stem from particular design elements of the EEfRT, or reflect a true gender disparity in normative effort-based decision-making.

In sum, this initial study unveiled a novel effort-based decision-making task, the 'EEfRT', as a means of exploring effort-based decision-making in humans. As an objective measure of individual differences in reward motivation, we believe the EEfRT may provide a useful tool for studying motivational anhedonia and its relationship to DA functioning.

CHAPTER V

DOPAMINERGIC BASIS OF EFFORT-BASED DECISION-MAKING IN HUMANS

To further demonstrate the utility of the EEfRT as a translational paradigm of reward motivation in humans, I next sought to demonstrate its association with neurobiological substrates that have been found to mediate motivation in animal studies. As reviewed in Chapter III, a wealth of preclinical data implicates DA as a crucial neurochemical for cost/benefit decision-making. Attenuation of DA signaling—especially in the NAcc—produces a behavioral shift away from HC/HR options (Cousins & Salamone, 1994; Salamone, et al., 2007), while enhancement of DAerigc tone increases willingness to work for rewards (Bardgett, et al., 2009). Similar effects have been observed for studies of risk-related choice, with DA blockade associated with reduced willingness to choose riskier (but larger) rewards (St Onge & Floresco, 2009), suggesting that alteration of DA neurotransmission may exert its influence primarily by helping the organism overcome response costs—such as effort requirements, probability of receipt or temporal delay— that may discount the face-value of the reward magnitude (P. E. Phillips, M. E. Walton, & T. C. Jhou, 2007; Salamone, et al., 2007).

Recently, two studies in humans reported similar effects of DAergic attenuation and potentiation on effort-based decision-making. In a sample of

smokers, dietary depletion of catecholamine precursors resulting in transient reduction of DA availability decreased the willingness to expend effort for cigarettes during a progressive ratio task (Venugopalan, et al., 2011). Conversely, a study performed using the EEfRT during a placebo-controlled, *d*-amphetamine challenge paradigm found that administration of *d*-amphetamine increased participants' willingness to make HC/HR choices, particularly under conditions of low probability (Wardle, Treadway, Mayo, Zald, & de Wit, 2011).

We evaluated individual differences in DA function by measuring stimulant-induced change in D2/D3 receptor availability using a placebo-controlled, *d*-amphetamine challenge paradigm in conjunction with a dual-scan.

Methods

Participants

25 participants (52% female) were studied as part of an ongoing investigation of individual differences in striatal and extrastriatal DA function. All participants were medically and psychiatrically healthy adults, age 19 to 29. Following initial screening, subjects were given an interview of their medical history and a structured psychiatric interview (SCID-NP). Subjects were excluded if they had any history of substance abuse, current tobacco use, and use of psychostimulants (excluding caffeine) more than twice in the subject's lifetime or at all in the past 6 months, any psychotropic medication for the past 6 months other than occasional use of benzodiazepines for sleep, history of psychiatric illness, significant medical condition, or any condition which would interfere in

PET or MRI studies (e.g., extreme obesity, claustrophobia, cochlear implant, metal fragments in eyes, cardiac pacemaker, neural stimulator, and metallic body inclusions or other metal implanted in the body, pregnancy). Participants were also excluded if they had any contra-indications for receiving *d*-amphetamine (abnormal EKG, hypertension). Subjects who reported recent use (within the last 6 months) of tobacco products were excluded. Subjects who reported recent use of alcohol or marijuana were allowed to continue in the study, provided that they abstained from any use of these substances until the study was complete. Urine drug screens were used to confirm drug abstinence over the course of the study. A summary of subject demographics is presented in table 1.

Table 1. Sample Demographics

Sex	52% Female, 48% Male
Race	76% Caucasian, 16% Asian-American, 8% African American
Age	Average: 21.8, Range: 18-29
Recent Tobacco Use (last 6 months)	0%
Recent Alcohol Use (last 6 months)	56%
Recent Alcohol Use (average consumption)	3 drinks per week (+/- 4.8)
Recent Cannabis Use (%)	12%
Recent Stimulants Use (%)	0%
Recent Hallucinogen Use (%)	0%
Recent Sedatives or Opioid Use (%)	0%
Past Alcohol Use	80%
Past Alcohol (average consumption)	4.6 drinks per week (+/- 5.8)
Past Cannabis Use (%)	24%
Past Stimulants Use (%)	4%
Past Hallucinogen Use(%)	4%
Past Sedative or Opioid Use (%)	0%

Study Design

The goal of the current study was to evaluate how variability in DA function was associated with individual differences in cost/benefit decision-making preferences. Subjects completed 3 testing sessions. The first two

sessions involved completing a PET scan while receiving either a pill placebo or *d*-amphetamine challenge. During the 3rd testing session, subjects completed the EEfRT as described previously. Importantly, subjects were *not* under the influence of *d*-amphetamine when completing the EEfRT. This design allowed us to assess how differences in DA system responsivity were associated with basal variation in cost/benefit preferences.

PET Image Acquisition

All PET images were acquired using [^{18}F]fallypride ((*S*)-*N*-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[^{18}F]fluoropropyl)-2,3-dimethoxybenzamide), a substituted benzamide with very high affinity to D2/D3 receptors (Mukherjee, Christian, Narayanan, Shi, & Collins, 2005). The use of [^{18}F]fallypride in the present context is critical in that unlike other D2/D3 ligands, [^{18}F]fallypride allows stable estimates of D2-like binding in both striatal and extrastriatal regions (Christian, et al., 2004; Mukherjee, et al., 2002). It thus provides a unique ability to simultaneously examine human DA function in both cortical and striatal areas involved in cost/benefit decision-making. Previous work has demonstrated good test-retest reliability of [^{18}F]fallypride measurements of non-displaceable binding potential BP_{ND} —a computed estimate of the number of available D2/D3 receptors—in both striatal and prefrontal areas (Mukherjee et al., 2002). Each subject received two [^{18}F]fallypride scans: the first was a baseline placebo scan, and the second scan occurred on a separate day and was performed while the subject received a 0.43 mg/kg oral dose of *d*-amphetamine. Scans were not

counterbalanced for several reasons. First and foremost, our study was designed to assess individual differences, and thus it was optimal to keep all aspects of the study design constant across subjects. Counterbalancing would require additional statistical control, and would lower statistical power. Moreover, counterbalancing would impair maintenance of blinding, as most subjects receiving *d*-amphetamine during the first scan would be aware of receiving placebo for the second scan. Finally, conducting the *d*-amphetamine scans on the first scan day requires additional time between scan days, which is problematic for scheduling female participants, who were scheduled so as to ensure that both scans were conducted in the early follicular phase of their menstrual cycle for both scanning days. All PET scans were acquired on a GE Discovery STE system manufactured by General Electric (Easton, CT, USA) located at Vanderbilt University medical center. [^{18}F]Fallypride was produced in the radiochemistry laboratory attached to the PET unit, following synthesis and quality control procedures described in US Food and Drug Administration IND 47,245. Scans were timed to start 3 hours after *d*-amphetamine administration, which was timed to coincide with the period of peak plasma *d*-amphetamine. 3-D emission acquisitions scans were performed following a 5.0 mCi slow bolus injection of [^{18}F]fallypride (specific activity greater than 3000 Ci/mmol). Serial scans were started simultaneously with the bolus injection of [^{18}F]fallypride and were obtained for approximately 3.5 hours, with two 15-minute breaks for subject comfort. Low dose CT scans were collected for attenuation correction prior to each of the three emissions scans.

PET Image Processing

Each subject's serial PET scans were first corrected for motion across scanning periods using a mutual information-based rigid body algorithm (Maes, Collignon, Vandermeulen, Marchal, & Suetens, 1997; Wells, Viola, Atsumi, Nakajima, & Kikinis, 1996). Regional D2/D3 BP_{ND} was calculated on a voxel-wise basis using the full (four compartment) reference tissue method (Lammertsma, et al., 1996), with cerebellum chosen as the reference region because of its relative lack of D2/D3 receptors (Hall, et al., 1994). The full model was selected over the simplified reference region model due to concerns that have previously been raised about applying the simplified model to high affinity ligands (Votaw, Kessler, & de Paulis, 1993). Using the full reference region method, near perfect ($r = 0.99$) correlations have been found with modeled estimates using a metabolite corrected plasma input function (R. M. Kessler, et al., 2000). Although this approach is slower computationally than the simplified (three parameter) tissue reference method, the two methods show nearly identical estimates of binding potential, and have demonstrated excellent convergence of modeled fits in regions with both high and low D2/D3 receptor levels. Voxelwise kinetic modeling was executed using Interactive Data Language (RSI, Boulder, CO).

Each participant's BP_{ND} image was aligned with their T1-weighted MRI based on co-registration of the weighted average of the PET dynamic scans to the MRI using a mutual information based rigid body algorithm (Maes, et al., 1997; Wells, et al., 1996). Prior to group analyses, a composite binding potential

image was created for each PET scan, and warped to MNI space using a non-rigid body co-registration (Rohde, Aldroubi, & Dawant, 2003). The transformation matrix from this warping was then applied to the BP_{ND} statistical parametric maps (SPM) in order to bring them into MNI space. Using the 'imcalc' routine as implemented in SPM5, voxel-wise maps of the percent change in D2/D3 BP_{ND} ($\%\Delta BP_{ND}$) across the amphetamine- and placebo-day scans were created for each subject, providing an index of stimulant-induced DA responsivity. Voxelwise $\%\Delta BP_{ND}$ maps were inspected for any regions showing $\%\Delta BP_{ND} > 50\%$, which could arise due to misalignment across scan days. One subject showed evidence of this in a few voxels near the boundary of the putamen and insula. Because the insula was among the areas showing statistically significant effects, we analyzed the data both with and without these voxels for the subject included in the analysis. The results were significant in both cases, and we report the lower magnitude effect (with those voxels excluded) below.

Statistical Methods

The effects of different levels of reward magnitude, probability and expected value (reward magnitude X probability) on the likelihood of making an HC/HR choice during the EEfRT were estimated using a single Generalized Estimating Equation (GEE) (Zeger & Liang, 1986). The relationship between individual differences in choice behavior and variability in $\%\Delta BP_{ND}$ was assessed on a voxel-wise basis using a multiple regression analysis as implemented in SPM5, with proportion of HC/HR choices as the primary independent variable and subject age

and gender included as covariates. We tested for regions showing both positive and negative correlations with proportion of HC/HR options. Whole-brain correction for multiple comparisons was achieved using a cluster-extent correction procedure as implemented in SPM5. Only results surviving cluster-correction ($p_{cluster} < 0.05$) are reported. Because [^{18}F]fallypride BP_{ND} values exhibit significant variability across different regions (e.g., striatum vs. PFC), we used variance estimates at the voxelwise level rather than the pooled variance used in typical parametric analyses (Dagher, 1998). Once significant clusters were identified, cluster-wise $\%\Delta BP_{ND}$ values were extracted and entered into SPSS 19.0 for further analysis.

Planned Analyses

Given the results of our prior study suggesting that the direct effect of *d*-amphetamine on EEfRT task performance was strongest for low (12%) probability trials (Wardle, et al., 2011), our first analysis was to identify associations between $\%\Delta BP_{ND}$ and the proportion of HC/HR choices during low probability trials. This condition requires willingness to pursue rewards when facing both effort and probability costs. This was followed-up by an exploration of the relationship between $\%\Delta BP_{ND}$ and proportion of HC/HR choices averaged across all probability levels, which examines individual differences in responses to effort costs alone.

Results

Behavioral Results

All subjects chose a combination of HC/HR and LC/LR options (mean proportion of HC/HR choices = 0.43, SD = 0.11). A single GEE model was used to test the effects of reward magnitude, probability and expected value on choice behavior. Consistent with results described in Chapter IV, each of these variables were significant, independent predictors of choice behavior: reward magnitude: b = 0.69, p = 0.001; probability: b = 1.03, p = 0.021; expected value: b = 1.16, p = 0.016.

DA Sensitivity and EEfRT Performance: Low Probability Trials Only

Based on our prior work indicating that the effects of *d*-amphetamine on EEfRT task behavior were strongest for low probability trials (in which subjects have to overcome costs related to both effort and low probability), I first explored associations between *d*-amphetamine-induced DA responses and proportion of HC/HR choices during low probability trials only. This analysis revealed a strong positive association between $\%\Delta BP_{ND}$ in left caudate (x = -8, y = 10, z = 14, peak Z-score = 3.45, k = 71, $p_{cluster} < 0.001$) (all coordinates are given in the imaging space of the Montreal Neurological Institute, MNI), primarily encompassing the pre- and post-commissural dorsal portion of this structure. In addition, HC/HR choices were positively correlated with $\%\Delta BP_{ND}$ within a prefrontal network comprised of bilateral ventromedial prefrontal cortex (vmPFC) (x = 20, y = 42, z = -18, peak Z-score = 3.67, k = 80, $p_{cluster} < 0.001$), left ventrolateral prefrontal

cortex (vlPFC) (x = -48 y = 18, z = 6, peak Z-Score = 3.13, k = 44, $p_{cluster}$ = 0.005). We also observed a positive association between $\%\Delta BP_{ND}$ in the left inferior temporal gyrus and HC/HR choices (x = -56, y = -18, z = -22, peak Z-score = 4.13, k = 41, $p_{cluster}$ = 0.018) (see table 2, figure 7).

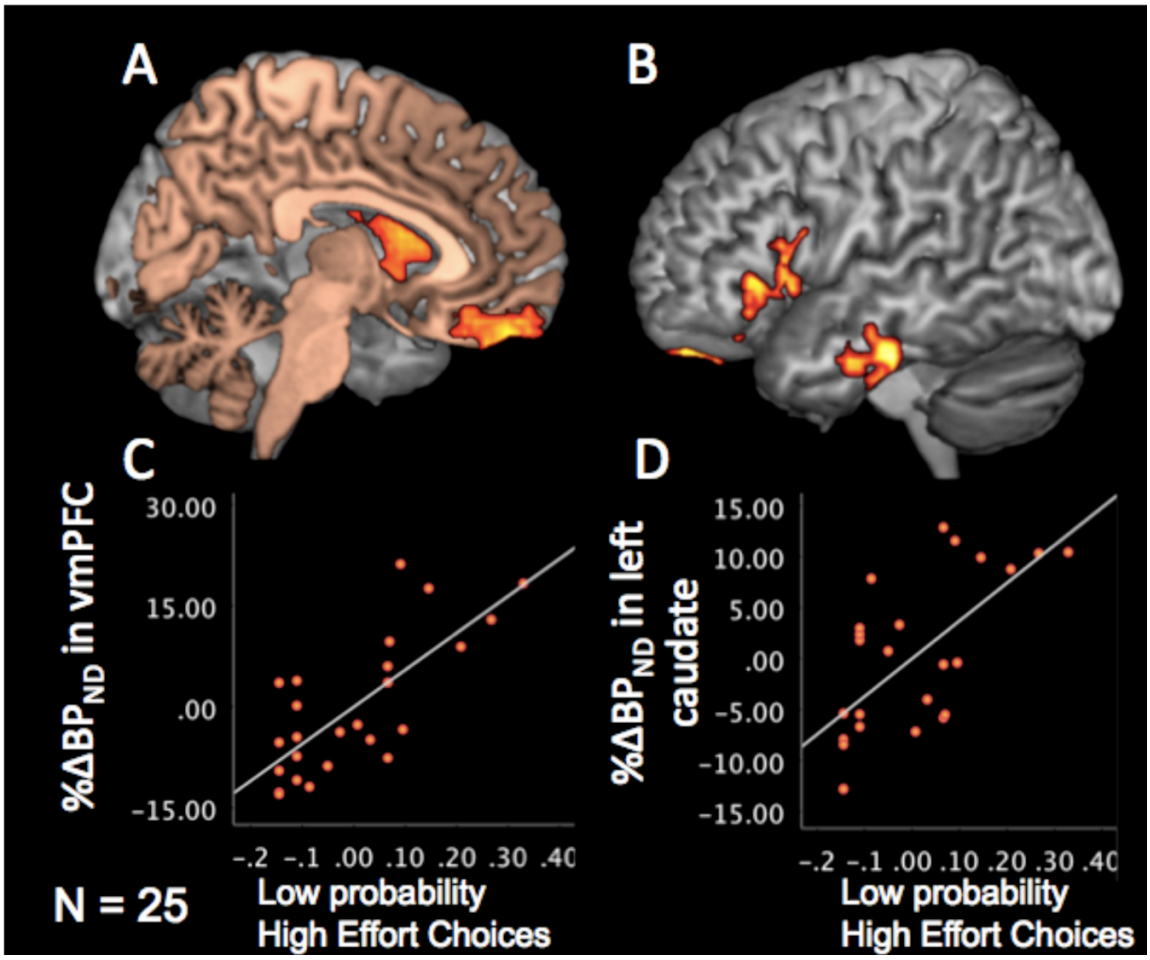

Figure 7: Relationship between proportion of HC/HR choices during low probability (12%) trials and stimulated DA release. **A.** SPM depicting voxels showing significant positive correlation between stimulated DA release in left caudate and vmPFC and proportion of HC/HR choices during low probability trials. **B.** SPM depicting voxels showing significant positive correlation between stimulated DA release in left vlPFC and temporal cortex and proportion of HC/HR choices during low probability trials. **C.** Scatterplot of proportion HC/HR choices during 12% trials and stimulated DA release in left caudate **C.** Scatterplot of proportion HC/HR choices during 12% trials and stimulated DA release in vmPFC. Visualization threshold reflects correction for multiple comparisons, t > 2.5, k >35.

For each of these identified regions, the association between DA responses and HC/HR choices was unchanged when the baseline BP_{ND} was included in the model as a covariate, thereby ruling out the possibility that the observed associations were due to individual differences in basal D2/D3 binding as opposed to $\%\Delta BP_{ND}$.

In order to assess the magnitude of stimulant-induced change in D2/D3 B P_{ND} in these indentified areas, we tested the effects of *d*-amphetamine on BP_{ND} within these regions. *D*-amphetamine produced a significant decrease in BP_{ND} in left caudate (-5.6%), left vlPFC (-7.6%), left temporal cortex (-4.2%), but not in vmPFC, which showed a non-significant decrease of -1.9% (see table 3). No regions showed a significant inverse correlation between $\%\Delta BP_{ND}$ and the proportion of HC/HR trials during the low probability trials.

Table 2. Voxel-wise correlations between EEfRT task performance and %ΔBPND

Region	peak coordinates x	y	z	peak Z-score	cluster-size (k)	cluster p-value (corr.)
Positive Correlations						
All Trials						
	-	-	-	-	-	-
Low Probability Trials						
vmPFC	20	42	-18	3.67	80	<0.001
Left caudate	-8	10	14	3.45	71	<0.001
vlPFC	-48	18	6	3.13	44	0.005
Inferior temporal gyrus	-56	-18	-22	4.13	41	0.018
Negative Correlations						
All Trials						
Left Anterior Insula	-24	22	10	5.55	206	<0.001
Right Anterior Insula	44	10	-2	3.41	50	0.022
Low Probability Trials						
	-	-	-	-	-	-

DA Sensitivity and EEfRT Performance: All Trials

In addition to exploring just the low probability trials, we also examined whether there were any associations between DA responses and the proportion of HC/HR choices averaged across all probability levels. When we tested for positive associations, we did not identify any clusters that survived correction for multiple comparisons. In the negative direction, overall proportion of HC/HR choices showed a strong inverse relationship with $\%\Delta BP_{ND}$ in bilateral anterior insula (Left: x = -24, y = 22, z = 10, peak Z-score = 5.55, k = 206; $p_{cluster} < 0.001$; Right: x = 44, y =10, z = -2, peak Z-score = 3.41, k = 50 $p_{cluster} = 0.022$), suggesting that greater DA sensitivity in these regions was associated with fewer HC/HR (i.e., more LC/LR) choices throughout the task (see table 2, figure 8). As above, we assessed whether the association between DA responsivity and HC/HR choices was affected by the inclusion of baseline BP_{ND} and found that it was not. We also explored the effects of *d*-amphetamine on BP_{ND} in the insular regions, and found that it produced significant decreases in BP_{ND} in both left and right insula, resulting in a -9.2% and -6.8% change, respectively (see table 3).

Table 3. Baseline and post-amphetamine BP_{ND} in all identified ROIs

Region	Baseline BP_{ND} Mean	Baseline BP_{ND} SD	AMPH BP_{ND} Mean	AMPH BP_{ND} SD	$\%\Delta BP_{ND}$	p-value
Left Caudate	15.3	0.02	14.5	1.61	-5.61%	0.00034
vmPFC	0.72	0.16	0.7	0.17	-1.92%	0.29573
vlPFC	0.67	0.12	0.62	0.14	-7.58%	0.00080
Inferior temporal gyrus	1.13	0.21	1.08	0.22	-4.15%	0.01077
Left Insula	3.81	0.46	3.46	0.48	-9.23%	0.00003
Right Insula	0.97	0.13	0.9	0.13	-6.83%	0.00162

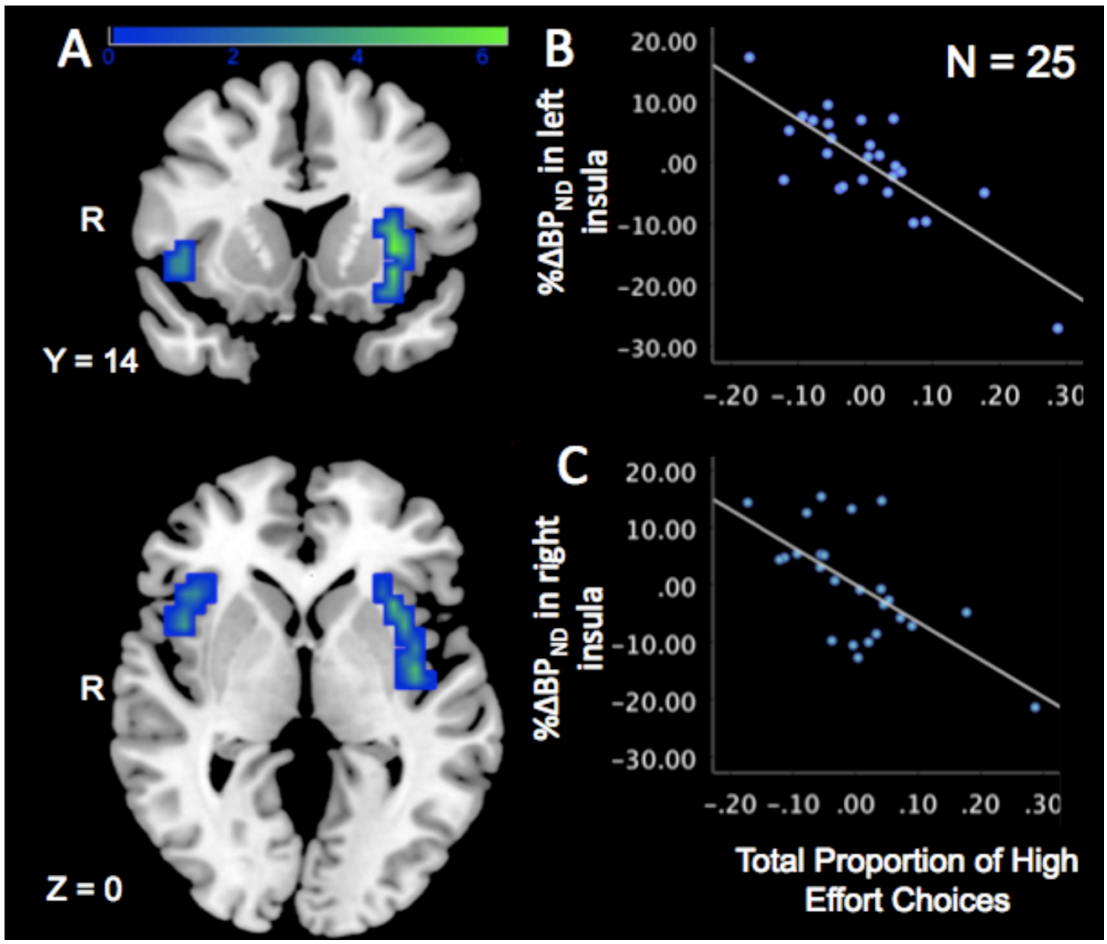

Figure 8: Relationship between proportion of HC/HR choices and insula DA release. **A.** SPM depicting voxels showing significant inverse correlation between DA release in bilateral insula and overall proportion of HC/HR choices. **B.** Scatterplot of DA release in left insula and proportion of HC/HR choices. **C.** Scatterplot of DA release in right insula and proportion of HC/HR choices. Visualization threshold reflects correction for multiple comparisons, t > 2.5, k >35. NB: Regression analyses are still significant when high-influence subject is removed (left: b = -0.64, p = 0.001; right: b = -0.53, p = 0.014).

ROI Analysis Across Probability Conditions

Given that distinct patterns of association emerged when examining HC/HR choices during low probability trials only as compared to HC/HR choices averaged across all probability levels, I extracted estimates of $\%\Delta BP_{ND}$ for all

identified regions and examined their association with the proportion of HC/HR choices for each level of probability (controlling for age and gender). In addition, I tested whether there was a statistically significant difference between correlations at different probability levels for each ROI (see table 4).

Table 4. Correlations and correlation comparisons for each probability level in all ROIs

Region	Probability Condition (pearson r)			Correlation Comparisons (t statistic)		
	88%	50%	12%	88% vs 50%	88% vs 12%	50% vs 12%
Left Caudate	-0.24	0.30	0.69***	2.11*	3.5**	1.67
vmPFC	-0.24	0.09	0.75***	1.32	3.98***	3.29**
L vlPFC	-0.13	0.27	0.71***	1.46	3.38**	2.45*
Inferior temporal gyrus	-0.21	0.27	0.64**	1.3	3.02**	2.24*
Left Insula	-0.48*	-0.63**	-0.24	-0.689	0.85	1.85
Right Insula	-0.47*	-0.46*	-0.16	0.52	0.91	0.59

*$p<.05$
**$p<.01$
***$p<.001$

Consistent with the voxel-wise approach, regions identified in our low-probability analysis (left caudate, vmPFC, left vlPFC and left temporal cortex) showed significant differences in r-values between the high and low probability conditions. The same was true for r-values compared between the low- and medium-probability conditions for all extrastriatal areas. In contrast, regions identified in the analysis of all trials (right and left insula) show no significant differences in r-values across any of the three probability levels.

Discussion

The present study provides novel evidence linking individual differences in DA responsivity to variation in human cost/benefit choice behavior. Positive

associations between DA function and willingness to expend effort for larger rewards were strongest during low probability trials, when subjects had to overcome both effort and probabilistic response costs. Two of the regions showing this association—the striatum and vmPFC—are known to be critically involved in multiple forms of cost/benefit decision-making (Botvinick, Huffstetler, & McGuire, 2009; Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009; Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008; Kable & Glimcher, 2009; McGuire & Botvinick, 2010). Interestingly, we also observed a strong inverse correlation between willingness to bear effort costs and DA responses in the bilateral insula. This pattern of findings suggests an important regional specificity in the relationship between DAergic function and individual differences in cost/benefit choice behavior.

In animal models, robust evidence indicates that DA-releasing agents help increase an organism's tolerance of costs that may discount the face value of a reward, such as effort required, (Salamone, et al., 2007), probability of receipt (St Onge & Floresco, 2009), or temporal delay (Wade, de Wit, & Richards, 2000). Further emphasizing the role of DA in specifically mitigating response costs, research has demonstrated that when effort or probability costs are low (e.g., effort requirements of an FR1 schedule), the impact of DA manipulation is minimal. However, the consequences of either DA enhancement or attenuation increase dramatically as response requirements rise and reward probabilities decline (Salamone, Wisniecki, Carlson, & Correa, 2001; St Onge & Floresco, 2009). Similarly in humans, the effects of *d*-amphetamine administration on

processing of effort and probability costs during the EEfRT are greatest for low-probability trials (Wardle, et al., 2011).

Consistent with these prior preclinical and human findings, we observed the strongest positive association between DA sensitivity and willingness to work more for rewards during low-probability trials, when subjects were required to overcome the maximum combination of effort and probabilistic response costs. In this analysis, we observed that DA responses in left striatum, as well as left vlPFC and bilateral vmPFC were associated with a higher proportion of High Effort choices. This corroborates prior findings suggesting that striatal DA function is critical for effort-related behavior (Salamone, et al., 2007).

In contrast to striatal DA, the role of DA within both vmPFC and vlPFC has received relatively less attention. Some evidence suggests that vmPFC DA function may be similarly required to maintain effortful responding for rewards (Cetin, Freudenberg, Fuchtemeier, & Koch, 2004), as well as motivated performance of cognitively-demanding tasks (Winstanley, et al., 2010). More broadly, the vmPFC has been heavily implicated in both human and non-human primate studies as a key region involved in value-based decision-making, in which the individual must choose across multiple cost/benefit options (Kable & Glimcher, 2009; Noonan, et al., 2010). Similarly, a number of studies also support a role for vlPFC in reward-based decision-making (McGuire & Botvinick, 2010; Sakagami & Pan, 2007). The current findings suggest that DA function within these regions contributes to individual differences in cost/benefit decision-making.

This study also identified the bilateral insula as a region where greater DA-responsivity was associated with more LC/LR (i.e., fewer HC/HR) options across all levels of probability. By averaging across probability levels, this analysis explored individual differences in sensitivity to effort-expenditure alone. To my knowledge, the effects of DA depletion or enhancement in this region on motivated behavior have not been explored in animals. However, both lesion and neuroimaging studies highlight the importance of this structure in mediating motivation and cost/benefit decision-making. Functional magnetic resonance imaging (fMRI) studies of reward learning have repeatedly highlighted bilateral anterior insula as an area involved in processing response costs (Knutson, Rick, Wimmer, Prelec, & Loewenstein, 2007; Kuhnen & Knutson, 2005) as well as reward-dependent prediction errors (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006), which are generally thought to reflect phasic DA activity (Schultz, 2007). Neural activity in the insula during anticipation of losses has been found to predict subsequent acquisition of loss-avoidance decision-making (Samanez-Larkin, Hollon, Carstensen, & Knutson, 2008), and individuals with lesions to anterior insula show less sensitivity to changes in expected value during risk-based decision-making (Weller, Levin, Shiv, & Bechara, 2009). Of particular note, a recent fMRI study exploring effort-based decision-making in humans found that increased bilateral insula activation was a strong predictor of choosing a Low Effort option (Prevost, Pessiglione, Metereau, Clery-Melin, & Dreher, 2010). While these studies do not directly assess DA function, it seems reasonable to speculate that these activation patterns may reflect—in part—DAergic signaling.

The human insula receives relatively rich DA innervation (Gaspar, Berger, Febvret, Vigny, & Henry, 1989) and expresses both D1-like and D2-like receptors (Hurd, Suzuki, & Sedvall, 2001). Support for this interpretation comes from another fMRI study in which subjects viewed positively and negatively-valenced cues predicting pleasant or aversive tastes (pictures of chocolate or moldy strawberries) while receiving either a pill placebo or oral dose of sulpride, a potent D2/D3-antagonist. Interestingly, sulpride blunted BOLD responses in the ventral striatum to chocolate pictures (positive cues), but also blunted BOLD responses in the anterior insula to moldy strawberry pictures (aversive cues) (McCabe, Huber, Harmer, & Cowen, 2011). These results support the interpretation of the present findings, that DA function in the striatum and vmPFC are associated with approach-related responses (increased motivation), while DA function in the insula may be associated with aversion. On the whole, these data, taken together with the current findings, raise the intriguing possibility that the insula plays a key role in processing response costs, and that DA signaling may contribute to this function.

Several limitations of this study warrant mention. First, while the analytical approach was informed by a previous study exploring the effects of *d*-amphetamine on EEfRT performance (Wardle, et al., 2011), the current study did not examine the effects of *d*-amphetamine on EEfRT behavior in this sample; this would be of interest, but would address a distinct question from the focus of the present work. A second potential concern is that the D2/D3 receptor ligand used in this study, [^{18}F]fallypride, is somewhat less sensitive to striatal DA release than

[^{11}C]raclopride (Morris & Yoder, 2007), which may have contributed to identifying fewer positive associations between EEfRT performance and DA responses in striatal regions than might be expected given past animal studies (e.g.(Salamone, et al., 2007)). Nevertheless, studies have consistently indicated that [^{18}F]fallypride is consistently able to detect significant *d*-amphetamine-induced displacement within the striatum (Cropley, et al., 2008; Morris & Yoder, 2007; Riccardi, et al., 2006; Slifstein, et al., 2010) and the magnitude of this release has repeatedly been found to show meaningful correlations with behavioral variables (Buckholtz, Treadway, Cowan, Woodward, Benning, et al., 2010; Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Woodward, et al., 2011). Another issue is the observation that between 12%-50% of subjects appeared to show negative $\%\Delta BP_{ND}$, depending on the region evaluated. Negative $\%\Delta BP_{ND}$ indicates an increase in D2/D3 receptor availability following *d*-amphetamine, which is inconsistent with the predicted effects of the drug. However, the presence of negative $\%\Delta BP_{ND}$ is common in past PET imaging studies across different ligands and regions, making it unlikely to reflect purely methodological error (Abi-Dargham, Kegeles, Martinez, Innis, & Laruelle, 2003; Drevets, et al., 2001; Leyton, et al., 2002; Martinez, et al., 2003; Volkow, et al., 1997). More likely, this reflects individual variability in the duration and magnitude of amphetamine responses, which would be consistent with studies of reported subjective effects (de Wit, Uhlenhuth, & Johanson, 1986). It is for this reason, however, that we interpret our data as reflecting DA "sensitivity" or "responsivity", rather than just DA release. We also note that the lack of counterbalancing in our

design could have impacted $\%\Delta BP_{ND}$ if the novelty of the first scan day differentially caused DA release relative to the second scan day, which would reduce the magnitude of calculated *d*-amphetamine BP_{ND} displacement. It is also theoretically possible that the administration of [^{18}F]fallypride during the first scan may have had effects on BPND that carried over to the second scan, though this seems unlikely given the sub-pharmaceutical dose used. Finally, there have been some questions regarding the ability of [^{18}F]fallypride to detect *d*-amphetamine-induced displacement of BP_{ND} in extrastriatal regions, particularly cortical areas (Cropley, et al., 2008; Slifstein, et al., 2010). However, a careful review of these studies indicates that *d*-amphetamine does in fact show expected decreases in [^{18}F]fallypride BP_{ND} across multiple areas, but variability is high in cortical regions, which diminishes the ability to detect a statistically significant effect of *d*-amphetamine in studies with modest samples.

In sum, this study provides further evidence linking variation in human DA function with cost/benefit decision-making in humans, and extends the results of the prior findings by demonstrating a distinct relationship with individual differences. This is a crucial step in validating animal models of DA function and effort-related behavior, and extends the translational value of these preclinical paradigms by demonstrating that they may be successfully translated to human paradigms.

CHAPTER VI

Motivational Anhedonia in Major Depressive Disorder

Having established the EEfRT as a translational measure of individual differences in motivation that was sensitive to inter-subject variability in DAergic function, the final aim of this dissertation is to test whether DA-linked motivational deficits are associated with MDD. To test this hypothesis, this final study recruited a sample of MDD patients and matched controls and compared their willingness to expend effort for reward as assessed by the EEfRT.

Methods

Participants

20 individuals diagnosed with MDD (14/20 female) and 15 healthy controls (9/15 female) participated. All participants were community volunteers who either responded to online recruitment advertisements or were referred from the Vanderbilt University Department of Psychiatry Mood Disorders Program outpatient clinic. Following initial screening, subjects were given an interview of their medical history and a structured psychiatric interview (SCID-P) (First, Spitzer, Gibbon, & Williams, 2005) and completed the Beck Depression Inventory II (BDI-II) (Beck, et al., 1996) and the Chapman Anhedonia Scales (Chapman, et al., 1976). For individuals in the MDD group, subjects were required to meet criteria for a current major depressive episode (MDE). Subjects were excluded if they met criteria for bipolar disorder, psychotic and schizoaffective disorders,

current substance abuse, past stimulant abuse, or past substance dependence. MDD subjects were also excluded for any current or past use of prescription drugs that act on DA (e.g., amphetamines, methylphenidate, l-dopa). Of the 20 participants in the MDD group, 17 subjects were on an antidepressant medication at the time of the study (15 SSRI alone, 2 SNRI alone). Additionally, 8 of the 20 subjects in the MDD group met criteria for a co-morbid anxiety disorder as assessed by the SCID.

Subjects in the control group were excluded if they met criteria for any current or past Axis I disorder other than specific phobia, past adjustment disorder, or past substance abuse of non-stimulants. Control participants were also excluded if they exhibited significant trait-anhedonia despite not meeting clinical criteria for an Axis I disorder as determined by a score on the Chapman Anhedonia Scales that was two-standard deviations higher than published normative data for this instrument (Chapman, et al., 1976). This exclusion was based on the results described in Chapter IV, showing that elevated trait anhedonia in a non-patient sample may reduce willingness to expend effort for rewards, and resulted in the exclusion of one potential control subject. No control subjects were on any form of psychotropic medication at the time of the study.

Measures

All subjects performed the Effort-Expenditure for Rewards Task (EEfRT or "effort") as described previously and completed the Beck Depression Inventory II

(BDI-II) (Beck, et al., 1996) and the Chapman Anhedonia Scales (Chapman, et al., 1976).

Statistical Analyses

Statistical analysis of choice behavior during the EEfRT was performed using Generalized Estimating Equation (GEE) models. The use of GEE is advantageous for the EEfRT, in that it can simultaneously model time-varying parameters (e.g., trial-wise changes in reward magnitude of the HC/HR option) as well as time-invariant parameters (e.g., estimates of stimulated DA release or MDD status). The use of GEE models is especially beneficial for the current study as they offer greater statistical power than traditional ANOVAS, which could compensate for the relatively smaller sample size of the current study as compared to the community sample described in Chapter IV. GEE models were implemented in SPSS 19 (IBM Armok, NY). The dependent measure was the dichotomous outcome of HC/HR or LC/LR choice, and we used a binary logistic distribution to model the probability of choosing the HC/HR option. Consistent with our prior analytical approach using the EEfRT, all GEE models included reward magnitude of the HC/HR option, probability and expected value (reward magnitude x probability). Separate models were computed to test the effects of group on HC/HR choices, as well as interactions between group and reinforcement variables (reward magnitude, probability and EV). All models included trial number as a nuisance covariate to control for possible effects of fatigue over the course of the task. For between-group analyses, models also

included any demographic variables where groups showed significant differences. For within-group individual differences analyses (e.g., using the Chapman scales), sex was included as a covariate, as sex has been shown previously to be a significant predictor of EEfRT task performance in individual differences analysis.

Results

Sample Characteristics

Subject demographics and clinical variables are included in table 5. The depressed and control groups did not differ in terms of sex (X^2 = .38, p = .537), or age (t_{33} = -.839, p = .41), but did differ in years of education (t_{33} = 3.00, p = .005), with the control subjects having approximately 2 more years of education on average. Subjects in the MDD group reported significantly higher depressive symptoms on the BDI-II (Mean = 24.6, SD = 9.25) than controls (Mean = 2.83, SD = 3.65) ($t_{26.2}$ = -9.57, p < .001). MDD patients also reported significantly higher scores on the Chapman Anhedonia Scales (Mean = 37.05, SD = 15.86) as compared to controls (Mean = 11.87, SD = 7.50) ($t_{28.6}$ = -6.23, p < .001).

EEfRT Trial Completion Rates

For both the MDD and control groups, all subjects chose a mix of HC/HR trials and LC/LR trials. There was no difference in the percentage of trials successfully completed by MDD patients (Mean = 99.4%, SD = 0.19%) or controls (Mean = 99.5%, SD = 0.15%) (t_{33} = .144, p = 0.89)

Table 5. Clinical and Demographic Characteristics

Meaure	MDD (n=20) Mean	SD	Controls (n=15) Mean	SD	p-value
Sex	14/20 female		9/15 female		0.64
Age	42.4	10.1	39.7	8.2	0.41
Years of Education	14.4	1.9	16.3	1.83	0.005
BDI-II	24.6	9.2	2.8	3.7	< 0.001
Chapman Anhedonia Scales	37.1	15.9	11.9	7.5	<0.001
Average Duration of Current MDE (months)	12.5	14.2	-	-	-
Average Number of Prior MDEs	2.3	1.3	-	-	-
Average Age of MDE Onset	39.5	10.6	-	-	-

Results of GEE Models

We tested six independent models GEE models. Each model included all experimental task variables, including reward magnitude, reward probability, expected value, and trial number. Because of group differences in years of education, all between-group models included years of education as a covariate. For within-group, individual difference models, gender was added as a covariate.

Model 1 tested for main effects of Group on preference for HC/HR options, and found that compared to controls, MDD patients were significantly less likely to make HC/HR choices (b = -0.79, $p < 0.001$) (see figure 9). The effect of group remained a significant predictor even when symptoms of psychomotor slowing—as assessed by SCID—were included as a covariate in the model ($p < 0.001$), indicating that the results were not explainable by depression-related differences in psychomotor speed.

In model 2, we tested for the presence of an interaction between Group and Reward Magnitude, and found a significant interaction (b = -0.379, p = 0.012). In follow-up within-group analyses, we found that while reward magnitude was a significant predictor of HC/HR choices for both groups, its effect was larger for controls (b = 0.694, p < 0.001) than for MDD patients (b = 0.437, p < 0.001). This suggests that the magnitude of the reward associated with the HC/HR option was more strongly predictive of choosing the HC/HR option in controls than in MDD patients.

Model 3 tested for an interaction between Group and Probability level. We observed a significant interaction between MDD patients and controls (b = -0.23, p = 0.038) such that probability was a stronger predictor of choice behavior for controls (b = 0.484, p < 0.001) then for patients (b = 0.361, p < 0.001).

In model 4, we tested for an interaction between Group and expected value, but did not find evidence for an interaction (b = -0.17, p = 0.399). However, while this interaction term was not significant, the expected value predictor showed a similar pattern to both reward magnitude and probability, such that it was a stronger predictor for the control group (b = 1.44, p = 0.03) as compared to the MDD group (b = -0.61, p < 0.001).

In model 5, we performed an individual differences analysis within the MDD group to see if EEfRT performance was related to symptom severity (BDI-II) and course of illness. In an initial model, we found that duration of the current MDE predicted significantly fewer HC/HR choices (b = -0.014, p < 0.001), while BDI-II scores were predicted more HC/HR choices (b = 0.027, p < 0.001). These

effects were both present when each of these predictors was included independently. We also note that sex was a significant predictor in this model, with men choosing more HC/HR choices than women.

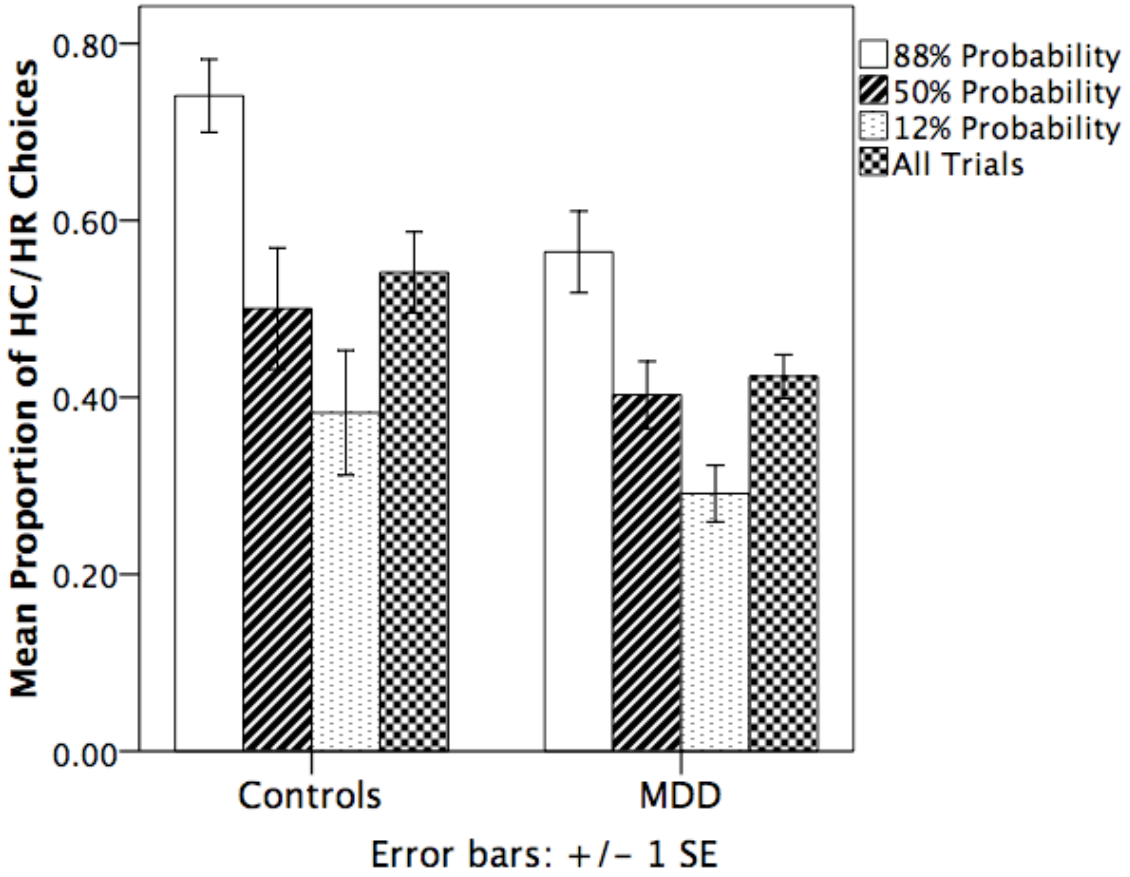

Figure 9: Mean proportion of HC/HR choices on the EEfRT for MDD patients and matched controls.

Given the unexpected direction of the relationship between BDI-II scores and EEfRT choices, in model 6 we followed up with item-level analysis of BDI-II items related to reward anticipation (item 2) and reported enjoyment (item 4). We found that reduced anticipation was inversely associated with HC/HR choices (b = -0.15, $p < 0.001$), while the opposite was true for deficits in enjoyment (b =

0.51, $p < 0.001$), suggesting that specific MDD symptoms may be differentially associated with EEfRT performance.

Discussion

In this final study, we found evidence that patients with MDD show motivational anhedonia as indexed by an objective, translational effort-based decision-making task. Individuals with current MDD were less willing to expend effort for the opportunity to earn larger monetary rewards as compared to healthy controls. This supports a growing body of evidence suggesting that motivation may be an especially crucial aspect of altered reward processing in MDD (Clery-Melin, et al., 2011; Sherdell, Waugh, & Gotlib, 2011). It may also help explain the success of behavioral activation treatments for MDD, which specifically target motivational symptoms (Dimidjian, et al., 2006).

In addition to differences in willingness to expend effort for rewards, we found that patients showed less sensitivity to information about the reward magnitude and probability of a win when making their choices. Prior studies have found associations between depression and sensitivity to reward probability (Forbes, Shaw, & Dahl, 2007; Gradin, et al., 2011; Pizzagalli, et al., 2008). This reduced capacity for integrating information about reward probability when making effort-related choices may be related to previously reported cognitive vulnerabilities regarding the prediction and expectancy of positive future events in MDD (Abramson, Metalsky, & Alloy, 1989). Despite these interactions with both probability and reward-magnitude, there was no interaction between group

and expected value. That said, while the interaction term was not significant, the expected value predictor did follow a similar pattern, such that it was a stronger predictor for controls as compared to patients.

Within the MDD group, we observed several associations between the EEfRT and clinical variables. First, duration of the current MDE predicted fewer HC/HR choices, even when controlling for current symptom severity. This may suggest that motivational deficits are associated with a poorer course of MDE. Although the causal direction of this relationship remains to be elucidated, it is interesting to note that cognitive vulnerability models of depression have posited that helplessness and hopelessness are causally associated more pronounced motivational deficits as well as a longer course of illness (Abramson, et al., 1989; Abramson, Seligman, & Teasdale, 1978). Unexpectedly, we additionally observed an overall positive association with current MDE symptom severity as indexed by the BDI-II and HC/HR choices. Using an item-level analysis, we found that reduced anticipation of positive future events was associated with less willingness to work for rewards, while the opposite was true for deficits in reward consummation. This may suggest that effort-mobilization is primarily linked to symptoms related to reward expectancy—consistent with prior reports (Sherdell, et al., 2011)—and highlights the presence of distinct sub-components of anhedonia. However, given limitations in the reliability of individual items, this analysis should be interpreted with caution. Replication studies will be required to further clarify the relationship.

The present study possesses several limitations. First, the requirement of speeded button-presses could affect choice behavior in some patients with psychomotor slowing. However, this seems unlikely given that patients and controls showed equal completion rates and controlling for psychomotor retardation did not alter the results. A second limitation of the current study is the inclusion of depressed individuals who were not free of antidepressant medications. Given known interactions between serotonin and DA, it is possible that SSRI medications may have influenced the current results. However, preclinical studies of SSRI effects on reward processing are mixed, with evidence to suggest that SSRIs both potentiate (Deslandes, Pache, Buckland, & Sewell, 2002; Muscat, Papp, & Willner, 1992) and attenuate (Hoebel, Hernandez, Schwartz, Mark, & Hunter, 1989) reward function, and that these effects may depend on whether an animal is in a depressive state (Markou, Harrison, Chevrette, & Hoyer, 2005). Given these inconsistent findings it is unlikely that medication status alone could explain group differences in EEfRT task performance. Moreover, our results are consistent with significant prior evidence that SSRI treatments fail to address symptoms related to motivation and anhedonia in MDD (Nutt, et al., 2007; Shelton & Tomarken, 2001). Finally, our control sample was screened to rule out high-levels of trait anhedonia, which may limit the specificity of our findings to MDD, as opposed to anhedonic traits.

In sum, the current findings demonstrate that reduced motivation and altered cost/benefit decision-making may be a crucial aspect of anhedonic symptoms. Additionally, the success of this translational approach highlights the

importance of incorporating preclinical models of reward processing into the conceptualization and assessment of clinical symptoms. Such measures may ultimately facilitate the development of a more objective nosology of reward-related deficits in MDD.

CHAPTER VII

SUMMARY AND GENERAL DISCUSSION

In this final section, I will begin by summarizing the arguments and empirical data described above, and then conclude with a general discussion, including the limitations of the present work as well as implications for treatment.

The guiding principle of this dissertation has been the need to identify sub-components of symptoms in MDD that may be tied to distinct neural circuits, with the ultimate goal of improving psychiatric nosology (Akil, et al., 2010). To this end, I have focused on the role of motivation for rewarding events in the clinical presentation of anhedonia in MDD, and its possible relationship to alterations in the mesocorticolimbic DA system. As outlined in chapter III, this neurotransmitter system has a long been associated with both reward processing and MDD, but its precise role in these phenomena are still being elucidated. From animal models, significant evidence has accrued to suggest that DA is specifically involved in the predictive value, incentive salience, and motivating properties of rewards (Berridge, 2007; Salamone, et al., 2007; Schultz et al., 1997). However, clinical measures of anhedonia (interview, laboratory and self-report), have generally neglected to assess these aspects of reward processing. Consequently, the focus of this dissertation has been to develop a laboratory-based measure that could be used to explore individual differences in reward motivation (as indexed by willingness to work for them) and test hypotheses

regarding the role of mesocorticolimbic DA function in motivation as well as the effects of clinical depression.

In Aim 1, I outlined the rationale for the design for the EEfRT and demonstrated the utility of this paradigm as a tool for assessing meaningful individual differences in motivation to spend effort for rewards among subjects. This task was then tested in a pilot sample of Vanderbilt undergraduates and community volunteers where it was found that individuals exhibited significant variability in their willingness to work for monetary rewards, and that some of this variance was attributable to self-reported levels of trait anhedonia. While this latter association was statistically significant, the effect size was moderate ($r = -0.30$). The absence of a stronger correspondence between reported hedonic responses and reward motivation is consistent with past studies exploring different sub-components of reward deficits (Strauss & Gold, 2012). Moreover, preclinical models suggest that neural systems encoding incentive salience and subjective pleasure are dissociable, albeit interacting. Consequently, it would be reasonable to predict that measures of reward motivation and hedonic responsiveness would be expected to show a non-zero positive association, without necessarily being very strong. This is also in keeping with behavioral reports in humans and animals demonstrating that various forms of behavioral or pharmacological manipulations can separably influence the motivational and hedonic properties of a given stimulus (Litt, Khan, & Shiv, 2010; Tindell, Smith, Berridge, & Aldridge, 2009).

In Aim 2, we used the EEfRT to explore DAergic correlates of individual differences in motivation using a dual-scan PET imaging protocol on and off a *d*-amphetamine challenge. Consistent with preclinical studies that heavily implicate ventral striatal DA function in motivation, we found that heightened DA responses to amphetamine in this region were associated with greater willingness to tolerate effort and probabilistic response costs. Somewhat surprisingly, we also observed an inverse association between DA release in the insula and EEfRT performance, such that greater DA predicted less desire to work for rewards. To my knowledge, no preclinical study has directly tested the role of insular DA function in the context of reward motivation. However, a number of functional neuroimaging studies have identified a role for the insula in the processing of responses costs and aversive stimuli and outcomes (Prevost, et al., 2010; Samanez-Larkin, et al., 2008), which may be modulated by pharmacological manipulation of DA (McCabe, et al., 2011). This finding is especially interesting given the multiple neuroimaging studies implicating the role of the insula in depression and anxiety (Mitterschiffthaler, et al., 2003; Paulus & Stein, 2006; Stein, Simmons, Feinstein, & Paulus, 2007; Strigo, Simmons, Matthews, Craig, & Paulus, 2008).

Finally, in Aim 3, I used the EEFRT paradigm to assess the role of motivational deficits in MDD. From this study, it was observed that MDD patients were less motivated for monetary rewards than controls, were less sensitive to reward information when choosing whether to expend more or less effort, and that the magnitude of these deficits were associated with the duration of the

current episode, which may indicate that motivational symptoms become more pronounced over time. This study suggests that anhedonia in depression does not simply reflect a reduced capacity to experience pleasure, and underscores the role of DA-linked motivational processing in MDD, which is consistent with prior evidence highlighting alterations in DA circuitry as part of the pathology of the disorder (Kumar, et al., 2008; Pizzagalli, et al., 2009l; Tremblay, et al., 2005).

Taken together, the results of these three studies stress the importance of addressing heterogeneity in the presentation of anhedonia, with the specific recommendation of identifying behavioral and neurobiological markers of "motivational anhedonia" as well as "consummatory anhedonia". In keeping with our primary set of predictions, we observed that individual differences in willingness to work were associated with DA function and the presence of MDD. Importantly, these findings included a specific association with DA function the striatum, thereby extending preclinical models of effort-based decision-making and ventral striatal DA function. As a result, the present work serves to enhance the relevance of these animal paradigms for research in clinical populations.

It is interesting to note, however, that while positive associations between DA responsivity and willingness to expend effort for rewards were observed only during the low probability trials, MDD patients did not appear to be specifically sensitive to reward probability. Rather, MDD patients showed an overall decrease in the willingness to expend effort across all three probability levels. Importantly, the only region to show a strong association between DA function an effort-choice across all 3 probability conditions was the insula, where DAergic

function was inversely related to willingness to work for rewards. This finding is particularly novel as no prior study has suggested the presence of this type of inverse relationship between individual differences in DA function and motivation or salience of rewards. Crucially, this suggests that DA may have directly oppositional roles in cost/benefit decision-making depending on the region of the brain engaged. Although not currently believed to play a central role in reward processing, the insula is well positioned to influence effort-based decision-making. In addition to direct DAergic input (Gaspar, et al., 1989), the insula exhibits reciprocal connections with the extended circuitry known to be involved effort-based decision-making, including the anterior cingulate (Augustine, 1996) the amygdala (Jasmin, Burkey, Granato, & Ohara, 2004; Reynolds & Zahm, 2005), vmPFC (Ongur & Price, 2000), and the ventral striatum (Reynolds & Zahm, 2005). Given the presence of fMRI studies suggesting that the insula may be involved in the anticipation of monetary losses, coupled with its known role in the representation of internal affective states (Craig, 2002, 2009; Naqvi & Bechara, 2009; Paulus & Stein, 2006; Phan, Wager, Taylor, & Liberzon, 2002), it seems plausible that DAergic signaling in the insula plays a specific role of encoding and predicting stimulus costs associated with rewards (Prevost, et al., 2010; Samanez-Larkin, et al., 2008). This function of the insula is especially intriguing in the context of decades old theoretical models that low expectancy for positive outcomes is a key factor in the development of depression (Abramson, et al., 1989; Abramson, et al., 1978; Alloy, Peterson, Abramson, & Seligman,

1984). Our data suggest that insular DA function might reflect a novel substrate underlying this critical cognitive vulnerability.

Implications for Treatment

The ultimate goal of improving our understanding of neurobiological mechanisms is to improve treatment. If the assessment of "motivational anhedonia" is improved, this could potentially serve as a key predictor of treatment response to specific types of behavioral or biological therapies shown to alter motivational systems. We do not believe that these treatments will necessarily work for all cases of depression, but suggest that they may be particularly effective for treatment-resistant depressions involving significant motivational anhedonia. This form of tailored treatment is the primary means of utilizing our enhanced knowledge of neurobiology to improve clinical outcomes, but it is dependent on detailed phenotypic description to be successful.

Behavioral activation (BA) provides a potential example of a specific psychotherapeutic technique that might be particularly appropriate in cases with motivational anhedonia. Initially developed as a component of Cognitive Behavioral Therapy (CBT), Behavioral Activation (BA) differs primarily in its conceptualization of patient cognitions as a ruminative behavior (Dimidjian, et al., 2006). The goal of treatment is to help the patient identify when they are engaging in rewarding and non-rewarding behaviors, and to help the patient make behavioral choices that are likely to increase exposure to positively reinforcing experiences.

Initial evidence suggests that by emphasizing an increase in motivated behaviors, BA may surpass CBT, particularly with clients diagnosed with co-morbid personality disorders (Coffman, Martell, Dimidjian, Gallop, & Hollon, 2007). Moreover, BA also includes specific techniques that address symptoms of decisional anhedonia. In one such technique, the therapist encourages the patient not to wait until the patient "feels like" engaging in a reward activity, thereby circumventing MDD-related impairments in reward decision-making due to lack of motivation (Martell, Addis, & Jacobson, 2001).

Recent evidence from neuroimaging studies also suggests that BA may specifically target the reward system. Whereas fMRI studies have shown that treatment response to CBT results in a progressive decrease in amygdala sensitivity to negative stimuli (Siegle, et al., 2006), successful treatment with BA led to increased BOLD responses of the striatum during reward anticipation (Dichter, et al., 2009). Additionally, specific techniques used in BA treatments also address components of decisional anhedonia.

In terms of pharmacological treatments, the exploration of tailored treatments for individuals experiencing motivational anhedonia using DA-active pharmacotherapies is recommended. This includes psychostimulants, DA agonists, and the NE/DA reuptake inhibitor bupropion. Of the current FDA approved antidepressant drugs with DA-acting properties, bupropion is the most widely used in clinical practice. However, the pharmacological profile of bupropion is complex, and its effects on reward processing in animals and

humans may rely on a variety of mechanisms, some of which are still not entirely known.

It is well established that bupropion has little direct effect on 5HT function (Stahl, et al., 2004). Several studies exploring bupropion occupancy of DAT at clinical doses have reported occupancy rates ranging from 14%-26% in the striatum (Kugaya, et al., 2003; Learned-Coughlin, et al., 2003; Meyer, et al., 2002), which are relatively low as compared to standard SERT occupancy rates of SSRIs (80%) or DAT occupancy of reinforcing psychostimulants (>50%) (Volkow, et al., 1995; Volkow, et al., 1997; Volkow, et al., 1998). These findings suggest that bupropion's direct ability to increase synaptic DA levels through blockade of DAT may account for only some of its antidepressant effects. However, more recent work has also shown that bupropion increases the activity of the intracellular vesicular monoamine transporter 2 (VMAT2) protein, which may enhance extracellular DA by increasing available DA in presynaptic pools (Rau, et al., 2005). Bupropion may also exert regionally-specific influence over DA function through its action as an inhibitor of the norepinephrine transporter (NET), which is the primary transporter of DA in prefrontal regions. Finally, more recent work has suggested that bupropion decreases the activity of nicotinic acetylcholine receptors, which play a role in the effects of bupropion on psychomotor symptoms in MDD (See (Dwoskin, Rauhut, King-Pospisil, & Bardo, 2006) for a review).

Preclinical studies have suggested that bupropion may be a superior treatment for symptoms of motivational anhedonia. Rats treated with bupropion

demonstrate decreased immobility time during the forced swim test and tail suspension tests (Cryan, et al., 2001; Cryan, et al., 2004) and showed greater willingness to work for food rewards during a progressive ratio task (Bruijnzeel & Markou, 2003). Moreover, the influence of bupropion was blocked via administration of both D1-like and D2-like receptor antagonists, suggesting that effects of bupropion were partially mediated through DAergic mechanisms (Paterson & Markou, 2007). Additionally, rats treated with either chronic or acute doses of bupropion show a reduced threshold for intracranial self-stimulation of the posterior lateral hypothalamus (Paterson, 2009; Paterson, Balfour, & Markou, 2007). Similarly, bupropion enhanced responding to a conditioned reinforcer (Palmatier, et al., 2009), although a separate study reported a bupropion-induced decrease in responding for sucrose (Reichel, Linkugel, & Bevins, 2008). The latter result is contrary to what would be expected, given the findings of (Bruijnzeel & Markou, 2003) and highlights the complex effects of the bupropion on reward processing. Interestingly, bupropion- mediated enhancement of conditioned reinforcers in the study by Palmatier et al. was ameliorated by Prazosin, an α_2-NE receptor antagonist, suggesting that bupropion's effects on reinforcement may also rely on noradrenergic mechanisms.

In addition to bupropion, psychostimulants, including dexamphetamine, methylphenidate and modafinil, have also been explored as both monotherapy and adjunctive treatment options for MDD. Results from these studies have not been encouraging (particularly in the case of monotherapy), although the majority of studies using psychostimulants were conducted several decades ago, before

either DSM criteria or the Feighner criteria were in place (for reviews, see (Orr & Taylor, 2007) and (Candy, Jones, Williams, Tookman, & King, 2008)), and fail to meet current methodological standards for clinical trials. More recently, however, interest has reemerged in the utility of psychostimulants as an adjunctive therapy for specialized populations. In patients with advanced terminal illness, where tolerance and abuse potential are less of a concern, psychostimulants have shown a positive response, though few of these studies were placebo-controlled (Orr & Taylor, 2007). Similarly, in elderly populations, which often show less responsiveness to traditional antidepressants (Paykel, et al., 1995; Reynolds et al., 1999) and exhibit higher rates of suicidality (Lebowitz, et al., 1997), citalopram augmentation with methylphenidate produced a positive and rapid treatment response (Lavretsky & Kumar, 2001). Finally, DA agonists such as bromocriptine, ropinirole and pramipexole also exhibit antidepressant properties (Cassano, et al., 2005; Corrigan, Denahan, Wright, Ragual, & Evans, 2000; Sitland-Marken, et al., 1990). In addition to treating depressed patients, pramipexole has also been shown to be successful in treating anhedonic and depressive symptoms in patients with Parkinson's disease, an illness associated with both loss of DA function and elevated rates of depressive illness (45%) (Lemke, 2008; Lemke, Brecht, Koester, Kraus, & Reichmann, 2005).

Overall, head-to-head clinical trials between DA-acting agents and other pharmacotherapies have revealed strikingly similar response rates in the case of bupropion and pramipexole, (Chouinard, 1983; Coleman, et al., 1999; Corrigan, et al., 2000; Croft, et al., 1999; Kavoussi, Segraves, Hughes, Ascher, &

Johnston, 1997; Mendels, et al., 1983; Thase, et al., 2005; Weihs, et al., 2000; Weisler, et al., 1994). For psychostimulants, response rates are usually significantly worse than other alternatives (Candy et al., 2008; Taylor & Orr, 2007). However, the potential role of DA-acting drugs as a superior treatment for anhedonic symptoms has received some empirical support. Bupropion has shown to be more effective at treating symptoms related to motivational and consummatory anhedonia (Bodkin, Lasser, Wines, Gardner, & Baldessarini, 1997; Tomarken, Dichter, Freid, Addington, & Shelton, 2004). In a large-sample review of treatment records of 910 patients receiving outpatient pharmacotherapy for depression, Jamerson and colleagues (2003) reported that patients receiving bupropion sustained release (SR) showed significant improvement of symptoms related to reduced interest, energy and loss of libido as compared to placebo (Jamerson, Krishnan, Roberts, Krishen, & Modell, 2003). Additionally, bupropion is often used to counter-act specific side effects of SSRIs (Nutt, et al., 2007), which may include reduced responsiveness to rewards and positive experience (McCabe C, 2009; Price, et al., 2009; Shelton & Tomarken, 2001). A recent meta-analysis of DA-acting antidepressant treatments suggests that they enhance overall quality-of-life in individuals with MDD (IsHak, et al., 2009). These findings are not only promising in terms of treatment options, they also further underscore the importance of tailoring DA-acting treatments to specific symptoms.

It should be noted that a limitation of DA-acting pharmacotherapies, however, is that they are regionally non-specific. Given that our results suggest

that enhanced DA in the anterior insula may be associated with reduced motivation, a global DA agonist may have limited therapeutic effects, and may depend heavily on individual differences in regional responses. Further efforts to isolate specific DA projection pathways—either pharmacologically or via electrodes—may be required to best address motivational anhedonia.

Limitations

While concerns regarding study-specific methodologies and designs have been discussed in the preceding chapters, there are nevertheless several general limitations that warrant additional comment. The first is the general lack of a simultaneous measure of affective responses to reward receipt during the EEfRT. While the current findings have been interpreted as evidence to suggest that motivational impairments may be present in MDD regardless of hedonic deficits, the studies included herein did not provide any clear evidence of this dissociation. It is therefore possible that MDD patients failed to work harder on the EEfRT simply because based on recent past experience (i.e., while depressed), they did not expect that the additional monetary rewards would lead to anything enjoyable. A recent study of effort-expenditure that used humorous cartoons as its primary rewards reported no difference in motivation between MDD patients and controls (Sherdell, et al., 2011). Importantly, Sherdell and colleagues collected affective ratings in response to the humorous cartoons, and found that both groups reported enjoying them to an equal degree. This may suggest that when presented with rewards that are valued similarly across

depressed and non-depressed groups, MDD patients are equally motivated to pursue them as controls. If true, such a result would suggest that decreased motivation is less impacted in MDD than would be suggested by the current findings. A related limitation is the reliance on monetary rewards as the only incentive used. Given that MDD in general and anhedonia in particular are often associated with diminished enjoyment of social rewards, as well as other forms of physical pleasure and sensation (e.g., reduced interest in sex), it could be argued that monetary rewards may not be fully representative of the breadth of rewarding experiences affected by anhedonia in MDD.

A second limitation is the complexity of the EEfRT task, which requires subjects to rapidly integrate information about effort expenditure, changing reward magnitudes and probability. As described in Chapter IV, the EEfRT was designed with several competing goals in mind, including translatability, relative ease of completion, ecological validity (e.g., inclusion of the probability manipulation) and resistance to optimization strategies. A concern of these design elements however, is that MDD is commonly associated with psychomotor slowing and deficits in concentration. Consequently, the EEfRT may be more cognitively taxing for patient populations, which might explain some of the apparent sub-optimal decision-making patterns exhibited by patients. Finally, while the overarching goal of this work has been to identify pathophysiological mechanisms of motivational deficits within patient populations, the studies described herein did not include a measure of DA function in an MDD sample. Rather, inferences are drawn regarding the role of

DA in motivational deficits in MDD primarily from the identification of DAergic correlates of EEfRT performance in healthy subjects coupled with the observation of behavioral deficits on this measure in patients with MDD. While the results reported to date are promising, the lack of a direct comparison curtails the interpretability of these findings.

Conclusions

Taken together, this work has sought to emphasize that anhedonia is a multifaceted construct, and that current clinical definitions and measures of anhedonia, which either fail to discriminate between motivational and consummatory aspects or ignore motivation altogether, are overly broad and underspecified for the purposes of pathophysiology. Much like the medical symptom of fever, anhedonia may have numerous manifestations and causes. To address this issue, we have recommended a general approach that seeks to reduce symptom-level heterogeneity by focusing on a particular, behavioral deficit (motivation) that both preclinical and clinical evidence suggests is linked to a specific pathophysiological mechanism (mesocorticolimbic DA). Through an integration of pharmacological, neuroimaging and clinical research methods with translational and “back-translational” approaches to assessment construction, the preliminary results of this program of research have been encouraging. Though clearly in its nascent stages, the findings reported above may eventually help personalize future treatments for anhedonia, and ultimately serve to reduce the overwhelming societal and individual costs of this debilitating symptom.

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