Functional Impairment and Presentations of Anhedonia in Major Depressive Disorder

by

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Abstract

Major Depressive Disorder (MDD) is associated with staggering global burden, largely due to impairments in occupational function. Evidence suggests that low motivation and effort levels, which are facets of anhedonia, significantly impact work quality. Despite anhedonia being a core MDD symptom, its relationship with functional impairment remains unclear. Anhedonia may manifest at a clinical, behavioural, and neurobiological level. Therefore, the goal of this study is to gain a better understanding of the link between occupational function and anhedonia in MDD using self-report measures, behavioural-tasks, and neuroimaging. Occupational impairment was significantly correlated with anhedonia severity on self-report measures and reward-tasks measuring effort, but not motivation. No significant correlation between resting-state connectivity and occupational function or anhedonia were found. These findings provide important insight into the complex relationship between function and anhedonia across multiple modes of analysis, which suggests that anhedonia is a potential treatment target to alleviate functional burden in MDD.

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List of Abbreviations

ACC:	Anterior cingulate cortex
ATHF:	Antidepressant treatment history form
BBR:	Boundary-Based Registration
BOLD:	Blood Oxygen Level Dependent
CRRT:	Cued-Reinforcement Reaction Time task
CRRT-RRS:	Cued-Reinforcement Reaction Time Task – Reinforcement-related speeding
DARS:	Dimensional Anhedonia Rating Scale
DLPFC:	Dorsolateral prefrontal cortex
DMN:	Default Mode Network
DSM-5:	Diagnostic and Statistical Manual of Mental Disorders
DTI:	Diffusion tensor imaging
DVS:	Desvenlafaxine
ECT:	Electroconvulsive Therapy
EEfRT:	Effort Expenditure for Rewards Task
FEAT:	FMRI Expert Analysis Tool
FLIRT:	FMRIB's Linear Image Registration Tool
fMRI:	Functional magnetic resonance imaging
FMRIB:	Functional Magnetic Resonance Imaging of the Brain
FNIRT:	FMRIB's Non-Linear Image Registration Tool
FSL:	FMRIB's Software Library
GABA:	Gamma-Aminobutyric Acid
gICA:	Group Independent Component Analysis
HAMD-17:	Hamilton Depression Rating Scale – 17 item
HPQ:	Health and Work Performance Questionnaire
ICA:	Independent Component Analysis
ICA-AROMA:	Independent Component Analysis – Automatic Removal of Motion Artifacts
LEAPS:	Lam Employment Absence and Productivity Scale

MCFLIRT:	Motion Correction using FMRIB's Linear Image Registration Tool
MDD:	Major Depressive Disorder
MDE:	Major Depressive Episode
MEI:	Motivation and Energy Inventory
MELODIC:	Multivariate Exploratory Linear Optimized Decomposition into Independent Components
MID:	Monetary Incentive Delay task
MINI:	Mini-International Neuropsychiatric Interview
MRI:	Magnetic resonance imaging
NMDA:	N-methyl-D-aspartic Acid
OFC:	Orbitofrontal cortex
PCC:	Posterior cingulate cortex
PFC:	Prefrontal cortex
PVC:	Positive Valence System
RDoC:	Research Domain Criteria
ROI:	Region of interest
rsfMRI:	Resting state functional magnetic resonance imaging
SDS:	Sheehan Disability Scale
SES:	Socioeconomic Status
SHAPS:	Snaith Hamilton Pleasure Scale
SMH:	St. Michael's Hospital
SN:	Salience Network
SNRI:	Serotonin and norepinephrine reuptake inhibitor
SSRI:	Selective serotonin reuptake inhibitor
STAR*D:	Sequenced Treatment Alternative to Relieve Depression
TE:	Echo Time
TEPS:	Temporal Experience of Pleasure Scale
TR:	Repetition Time
UHN:	University Health Network

UPSA:	University of California San Diego Performance-based Skills Assessment
VLPFC:	Ventrolateral prefrontal cortex
VMN:	Ventromedial Network
VMPFC:	Ventromedial prefrontal cortex
WHODAS:	World Health Organization Disability Assessment Schedule

Chapter 1

Literature Review

1.1 Major Depressive Disorder

There are over 350 million individuals affected by Major Depressive Disorder (MDD), which is a leading cause of global disability (World Health Organization, 2017). MDD is associated with significant personal burden, which contributes to greater societal and economic burden (Lam et al. 2016; World Health Organization, 2017). In Canada alone, there is an annual and lifetime prevalence of 4.7% and 11.3% of MDD, respectively (Lam, Parikh, et al., 2016; Patten et al., 2015). Furthermore, in 2016, the Conference Board of Canada estimated that the annual cost of depression to be over $30 billion, particularly due to reduced work productivity (Conference Board of Canada, 2016).

To meet criteria for a Major Depressive Episode (MDE), the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) states that an individual must report at least five symptoms of depression for at least two weeks, which significantly impact the individual's functioning (American Psychiatric Association, 2013). However, at least one of two core symptoms must be present: low mood or anhedonia (i.e. loss of interest or pleasure). Other diagnostic criteria include: significant weight loss/gain, appetite disturbances, fatigue or loss of energy, decreases in concentration, feelings of worthlessness, diminished ability to concentrate, insomnia/hypersomnia, suicidal ideation and psychomotor retardation/agitation (**Table 1;** American Psychiatric Association, 2013; Parikh et al., 2016). In addition to these depressive symptoms, functional impairment is also included as a diagnostic criterion for MDD.

Table 1. DSM-5 Diagnostic Criteria for Major Depressive Disorder

1. **Depressed mood, feelings of sadness, most of the day nearly every day**
2. **Loss of interest or pleasure in all, or almost all activities**
3. Loss of weight/appetite or gain of weight/appetite when not dieting
4. Psychomotor retardation/agitation
5. Fatigue or loss of energy
6. Feelings of worthlessness or excessive or inappropriate guilt
7. Diminished ability to think or concentrate, or indecisiveness
8. Recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt
9. Insomnia/hypersomnia

* bolded depressive symptoms are core criteria for the diagnosis of MDD

The heterogeneity of these depressive symptoms has made the study and treatment of MDD a significant challenge and has contributed to the high relapse rates and prevalence of treatment-resistance (McKnight and Kashdan, 2009). Importantly, the complexity of MDD has important implications for the associated functional impairment that arises (Bortolato et al., 2016). Function describes the ability of an individual to complete their daily tasks in a manner that is satisfactory to them (Lam et al., 2016). Despite functional impairment being highly prevalent and contributing significantly to the burden associated with MDD, it has received disproportionately less attention in the research literature than depressive symptoms (Lam et al., 2016; McKnight and Kashdan, 2009). As a result, functional impairment, specifically in the occupation domain will be the focus of this thesis and will be described in greater detail in the following sections.

1.2 Functional Impairment in MDD

1.2.1 Burden of Functional Impairment in MDD

The burden associated with MDD is largely due to the high prevalence and severity of functional impairment (World Health Organization, 2017). In a study by Kesler and colleagues, they determined that a staggering 96.9% of patients with MDD had functional impairment in at least one area of their lives (Kessler et al., 2003). More specifically, a significant proportion of the economic and societal burden of MDD is a result of increased workplace presenteeism and absenteeism (Greenberg et al., 2015; Lam, Iverson, et al., 2016). For example, approximately 59% of MDD-related costs in Europe are associated with reduced workplace productivity (World Health Organization, 2017). In another study of workplace depression, individuals with MDD missed approximately 8% of work hours and experienced a 35.2% reduction in productivity (Sato & Yeh, 2013).

Notably, despite over 60% of patients entering clinical care with moderate to severe functional impairment, a significant proportion of individuals continue to experience some level of functional impairment after receiving treatment (Iorfino et al., 2018). These residual impairments in function are associated with greater risks of relapse, which have several implications in the adequate treatment of depression (McKnight & Kashdan, 2009). Since current treatment regimens and remission criteria focus on symptomatic improvements, the high rates of relapse and residual symptoms may be, at least in part, a result of failing to adequately treat functional impairment (Bortolato et al., 2016). In fact, several studies have reported a strong negative correlation between severity of functional impairment and remission rates (Culpepper, Lam, & McIntyre, 2017; Jha et al., 2019; McKnight & Kashdan, 2009). Jha and colleagues noted that after 6-weeks of treatment, only 15.5% of MDD patents with moderate-to-severe functional impairments achieved remission in contrast to 66.7% of patients with minimal impairments (Jha et al., 2019). Furthermore, while it is clear that depressive symptoms contribute significantly to functional impairment, there is substantial evidence which suggests that they are overlapping, but distinct constructs, which emphasizes the importance of addressing function independently (Kennedy et al., 2019; Lam et al., 2017;

Milanovic, Holshausen, Milev, & Bowie, 2018; Sheehan et al., 2011; Xiao et al., 2018). However, in MDD clinical studies, functional impairment is often not evaluated or is a secondary treatment outcome, which limits our current understanding of its development and consequences. In summary, these data, which will be discussed in more detail below, highlight a strong rationale to shift greater attention towards the study and treatment of function in MDD in order to alleviate its global and personal burden.

1.2.2 Overview of Functional Impairment in MDD

As mentioned, functional impairment in MDD is highly prevalent, with some studies reporting that approximately 40% of patients experience moderate to severe impairment (Jha et al., 2019). The underlying etiology of functional impairment is heterogeneous. Each case of MDD has an array of contributors with respect to socioeconomic factors, symptoms, and comorbidities, which cumulatively can have varying impacts on patients' function (Beck et al., 2011; Kennedy, Foy, Sherazi, McDonough, & McKeon, 2007; Lam et al., 2012). For example, education level, previous hospitalizations, age and cognitive dysfunction may disparately impact the trajectory of social and occupational functioning changes after treatment (Iorfino et al., 2018; Levada & Troyan, 2019).

Several treatment studies have reported that improvements in function consistently lag behind depressive symptoms (Lin, Chou, Chen, & Chen, 2015; McCall, Reboussin, Cohen, & Lawton, 2001; McKnight & Kashdan, 2009). For example, Lam et al. found improvements in function after 4 weeks of desvenlafaxine treatment, in contrast to 2 weeks for depressive symptoms. The authors concluded that several months may be required for meaningful changes in function to arise (Lam et al., 2014). Additionally, Jha et al. (2019) analyzed data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a large antidepressant treatment trial to assess real-world effectiveness, and determined that function improved independently of depressive symptoms after acute treatment (Jha et al., 2019).

Functional remission is commonly defined by the Sheehan Disability Scale (SDS), a widely used measurement of function (Sheehan et al., 2011). A total score of 6 or less and

subscale scores of 2 or less are indicative of functional remission. Importantly, functional remission may occur less frequently than remission of depressive symptoms, with the former at 32% and the latter at 38% in some pooled analyses (Lam et al., 2014, 2017; Milanovic et al., 2018; Sheehan et al., 2011; Xiao et al., 2018). Furthermore, remission of both depressive symptoms and function occurs less frequently than either alone (Kennedy et al., 2019). For example, 24% of MDD patients treated with escitalopram for 8 weeks achieved functional remission while only 18% achieved combined symptomatic and functional remission (Kennedy et al., 2019). Similarly, in the STAR*D trial after 6 weeks of treatment, depression remission rates were significantly lower in patients with baseline moderate-to-severe functional impairment (15.5%) than those with no to minimal impairment (66.7%) (Jha et al., 2019). The above findings suggest that functional impairment has a longer trajectory to improvement with antidepressant treatment or that antidepressants may not adequately target functional impairment. They also suggest that the severity of functional impairment prior to treatment may be a useful predictor of acute treatment outcomes and remission, which is reported in other studies as well (Dennehy, Marangell, Martinez, Balasubramani, & Wisiniewski, 2014; Jha et al., 2016). It is important to note that cut-off scores for functional remission have only been determined for the SDS, and not other function scales. This makes comparisons across studies more difficult. Therefore, more studies are required to refine the definition of functional remission, which would also then inform what is considered functional remission in MDD.

Notably, while patients who achieve remission of depressive symptoms often have better functioning relative to responders, their functioning continues to be significantly worse than the general population (Sacchetti et al., 2015). Furthermore, McKnight and Kashdan determined that among MDD patients, residual impairments in function were associated with greater relapse risk, which is likely to significantly impact their quality of life (McKnight & Kashdan, 2009). Indeed, while MDD remission is currently defined relative to depressive symptoms, this is not in line with patients' perspectives on what constitutes remission. It is a misconception that patients primarily prioritize symptom resolution during treatment. Instead, patients consistently rank the restoration of premorbid functioning higher (Demyttenaere et al., 2015). Zimmerman and colleagues redefined MDD remission from the patient perspective by

having them rank outcomes which they believed encompassed remission (Zimmerman et al., 2006). Out of the 16 outcomes, the ability to 'return to usual level of functioning at work, home, or school' was rated as 'very important' by 74.3% of patients, placing it third in the list with 'Presence of positive mental health (e.g. optimism, self-confidence) and 'Feeling you're your usual, normal self' above it (Zimmerman et al., 2006). This highlights the importance of patient perspectives during the treatment process. McKnight and Kashdan suggest that while symptoms may be an early indicator of treatment response, improvements in function represent meaningful change for patients (McKnight & Kashdan, 2009).

1.2.3 Functional Competence and Functional Performance

Functional impairment is multidimensional in its manifestation, causes, and treatment. However, the current gold standard for the measurement of function, the SDS, is limited to three items which may fail to capture the complexity and specificity of functional impairment in MDD (Leon, Olfson, Portera, Farber, Sheehan, 1997). Having a better conceptualization of the etiology and assessment of function, as both an outcome and predictor of remission, may offer insight into addressing treatment resistance, improving patient quality of life and guiding future research in MDD. The impairments in real-world function that patients with MDD experience may be similar, however, this may stem from disparate levels of functional competence and/or functional performance (Gupta, Bassett, Iftene, & Bowie, 2012; Milanovic et al., 2018). Functional competence, also known in the literature as functional capacity, describes the objective capabilities of an individual to complete specific activities when tested in isolation, such as in laboratory settings (Milanovic et al., 2018). Functional performance describes an individual's perception of their ability to function, which can impact their ability to translate their functional competence into real-world settings (Gupta et al., 2012; McClure et al., 2007).

While functional competence often translates to real-world functioning, there are several instances where this may not be the case (Milanovic et al., 2018). Competency in several domains of function may be required for adequate real-world function. Furthermore, a MDD patient may have the appropriate competency to function in real-world settings, however, their impaired functional performance may inhibit them from doing so (Cardenas et

al., 2013; Milanovic et al., 2018). For example, presenteeism may result from a combination of reduced competency or performance level (Cardenas et al., 2013).

Impairment in functional competence and performance may be a result of depressive symptoms such as low motivation, cognitive ability, poor stress management and increased reactivity to stress (Adams, Balbuena, Meng, & Asmundson, 2016; Cha et al., 2017; Jerez-Roig et al., 2016; Karpov et al., 2017; Zajecka, Kornstein, & Blier, 2013). However, these symptoms may have a differential impact on a patient's functional competency and performance. Functional competence may have a greater relationship with objective cognitive deficits involved with working memory and attention (Bowie, Gupta, Holshausen, et al., 2013). In contrast, functional performance may be linked to reduced self-efficacy and subjective impairments in cognition. In a study by Milanovic et al., the authors reported decreased functional competency in patients with MDD compared to healthy controls; specifically in finances and communication, but not in planning and transportation (Milanovic et al., 2018). Patients with MDD underestimated their functional abilities, believing they performed significantly worse on the task than they did, which may translate to reduced functioning in real-world situations. Furthermore, this poor perception of their ability to complete the task was significantly correlated with actual task performance. In contrast, healthy controls were able to gauge their performance more accurately on the task, and they were more able to assess how they function in real-world situations.

1.2.4 Domains of Function

When describing functional impairment in patients with MDD, it can be within the context of their global function or within specific domains. Currently, the most predominantly studied domains in MDD are the occupational and social domains, largely due to their prevalence and more tangible impacts on MDD-related burden (Beck et al., 2011; Greenberg et al., 2015; World Health Organization, 2017). It is important to recognize that functional impairment may affect several domains simultaneously or independently. Functional domains can span across a wide range of areas including education, completion of daily chores, organizational and planning capabilities, physical functioning, and family functioning. These

domains may be impacted to various degrees in each case of MDD, with different underlying etiology, manifestations, and responsiveness to treatments. There are several psychological, social, and biological factors involved with MDD which may differentially impact function both globally and within domains (Kikuchi, Suzuki, Uchida, Watanabe, & Mimura, 2013; Lam et al., 2012; Watanabe et al., 2017). Taken together, these factors contribute to the complex nature of functional impairment in MDD and will be discussed in more depth in the following section.

1.3 Contributors to Functional Impairment

Functional impairment is heterogenous with varying levels of severity and domains affected. While the number of contributing factors is vast, their respective impact on function, as well as the knowledge base of each factor, differs. Since the empirical study of function in the context of MDD is relatively nascent, an in-depth understanding of the direct impact of these factors on function is limited. Some of the more-well studied contributors, include depressive symptom profile, cognitive impairments, sleep disturbances, fatigue, as well as low self-esteem, efficacy, energy, and motivation, all of which will be discussed in greater detail below. This will allow for a better understanding of the literature and the key gaps in our current knowledge that will ultimately provide important context for the present study.

Depressive Symptom Profile

There is substantial evidence that depressive symptoms have a significant impact on functional impairment. In a review by Greer and colleagues (2010), they found that increased severity of depressive symptoms was associated with greater functional impairment across several domains, including occupational and social function. However, evidence suggests that symptom severity has disparate impacts on each functional domain (Aikens, Kroenke, Nease, Klinkman, & Sen, 2008; Fervaha, Foussias, Takeuchi, Agid, & Remington, 2016). In a study by McIntyre and colleagues (2015), they observed that variability in global function was explained by depressive symptom severity to a greater extent than cognitive difficulties (McIntyre et al., 2015). In contrast, variability in work quality was explained to a greater degree by cognitive difficulties over depressive symptom severity (McIntyre et al., 2015). Several studies have

reported that depressive symptom severity accounts for 13-42% of the variance explaining functional impairment, depending on the functional measure and domain assessed (Fervaha et al., 2016; Karsten, Penninx, Verboom, Nolen, & Hartman, 2013; Verboom et al., 2011). This wide range of variance suggests that factors other than general severity of depressive symptoms may play a key role in function.

In the National Institute of Mental Health Collaborative Depression Study over the course of 10 years, Judd and colleagues examined the changes in monthly ratings of function in MDD patients with varying levels of symptom severity (Judd et al., 2000). Consistent with other studies, they reported a chronic impairment of function that correlated with depression symptom severity even in patients with subthreshold levels. However, this impairment was absent in patients who became asymptomatic, which strongly suggests that residual symptoms are a significant contributor to functional impairment (Judd et al., 2000). Several studies have reported persistent functional impairment associated with residual symptoms (Kennedy et al., 2007). Nil and colleagues observed that after treatment with escitalopram, 50% of patients who had residual symptoms continued to experience impaired function (Jae, Ylana, Jin, Seung, & Dominique, 2016; Jerez-Roig et al., 2016; Nil, Lütolf, & Seifritz, 2016; Zajecka et al., 2013). Furthermore, evidence also demonstrates that patients with subthreshold levels of depressive symptoms have similar levels of impaired social functioning as patients with MDD (Kennedy et al., 2007).

With respect to specific depressive symptoms, cognitive deficits, motivational deficits, low energy and mood may have the most robust impact on functional impairment (Fervaha et al., 2016; Tam & Lam, 2012). While studying the trajectories of several treatment outcomes, Aikens and colleagues observed that occupational and social function both improved with mood, albeit at a slower rate (Aikens et al., 2008). However, social function improved at a faster rate than occupational function, which may be indicative of a stronger relationship between social function and mood (Aikens et al., 2008). Given the spectrum of symptoms in MDD, it is essential for future research to understand their differential impact on function.

Cognitive Impairments

An individual's cognitive status is predictive of their functional capabilities, globally and within domains, even after controlling for other depressive symptoms (Bowie, Gupta, & Holshausen, 2013; Jaeger, Berns, Uzelac, & Davis-Conway, 2006; Mcintyre & Lee, 2016). Certain cognitive deficits, within areas such as attention, executive function and verbal memory, are more consistently associated with functional impairment, even after remission (Jae et al., 2016; Woo, Rosenblat, Kakar, Bahk, & Mcintyre, 2016). In a study by Levada and Troyan (2019), they reported that among patients with MDD, reduced concentration was a significant predictor of overall function, occupational function and social function, but not family function. Occupational function, but not the other domains, was also associated with delayed recognition, working memory, and attention (Levada & Troyan, 2019). These findings, and those of other studies suggest that occupational function may be more sensitive to changes in cognition.

Cognitive deficits may also impact function via objective or subjective impairments (Cha et al., 2017; Miskowiak, Vinberg, Christensen, & Kessing, 2012). In a study by Gupta and colleagues, they reported that while both objective and subjective cognitive impairments worsened function, there is evidence that this occurs via different mechanisms (Gupta et al., 2013). Objective cognitive impairments were associated with an inability to complete certain tasks that are required for function. In contrast, patients with subjective cognitive impairments often had the ability required to complete certain tasks, but this did not translate to real-world functioning (Gupta et al., 2013). Subjective cognitive impairments may also have an independent effect on function over depressive symptoms or objective cognitive impairment. McIntyre and colleagues determined that MDD severity accounted for 37% of the variance of global function and subjective cognitive inattention accounted for 38% of workplace productivity and quality (McIntyre et al., 2015). When the effects of inattention and depression severity were isolated, inattention had a greater impact on occupational function but lower impact on global function (McIntyre et al., 2015). Furthermore, since cognitive deficits tend to persist following symptomatic remission, it may be a highly effective treatment target for chronic functional impairment (Mcintyre & Lee, 2016). However, while several studies

demonstrated that subjective cognitive ability had greater impacts on overall function and in multiple domains, objective cognitive ability was not a significant predictor in some studies (Cha et al., 2017). Nevertheless, cognitive impairment, both subjective and objective, appears to have a strong association with functional impairment in MDD.

Low Self-Efficacy and Self-Esteem

MDD patients commonly experience low levels of self-efficacy and self-esteem which may impact function through direct or indirect avenues (Cardenas et al., 2013; Shimotsu & Horikawa, 2016). In the context of function, healthcare professionals and researchers oftentimes focus on the objective capabilities of MDD patients and often attribute them as a primary contributor of functional impairment (Zimmerman et al., 2006). However, Cardenas and colleagues reported that low self-efficacy may play a role in impaired function by mediating the relationship between an individual's functional competence and functional performance (Cardenas et al., 2013). They reported that they were significantly related only when self-efficacy was high (Cardenas et al., 2013). Interestingly, no relationship between functional competence and functional performance were identified in patients with low self-efficacy in any tested domain of function (Cardenas et al., 2013). The authors suggest that reduced self-efficacy may explain why individuals may have the ability to complete the behaviours necessary to function, but lack the confidence to translate these to real-world settings (Cardenas et al., 2013).

Other studies have reported that self-efficacy may have a mediating effect between perceived stigma and function (Picco et al., 2017; Shimotsu & Horikawa, 2016; Yeh, Lee, Sung, & Tung, 2014). Although the stigma of mental illness is still prevalent, patients with MDD often overestimate the degree of this stigma, often resulting in internalized stigma (Pattyn et al., 2014). Patients with higher internalized stigma were more likely to have poor functioning, globally and within social, occupational, physical and school domains (Picco et al., 2016; Yen et al., 2009). According to the current literature, high levels of internalized stigma appears to have an impact on function via reduced levels of self-efficacy and self-esteem (Picco et al., 2017; Shimotsu & Horikawa, 2016). There is also evidence that the impact of this relationship varies in

the context of different functional domains. Picco and colleagues observed that self-efficacy significantly mediated the relationship between perceived stigma and impairment in physical function but not social function (Picco et al., 2017). With non-remitters frequently reporting lower levels of self-efficacy, there is merit in targeting these negative beliefs in order to improve function (Yeh et al., 2014).

Sleep Disturbances

Sleep disturbances, such as insomnia and sleep latency, are common symptoms of MDD which contribute significantly to functional impairment (Greer et al., 2010; Lai et al., 2014; Xiao et al., 2018). MDD patients with insomnia have demonstrated poor overall function, and in the occupational and social domains (O'Brien et al., 2011; Rungpetchwong, Likhitsathian, Jaranai, & Srisurapanont, 2017). In a study by O'Brien and colleagues, they noted that severe insomnia was associated with poorer social functioning over a five-year span (O'Brien et al., 2011). Interestingly, there is evidence that treatments that target insomnia may result in greater restoration of function (Norell-Clarke, Jansson-Fröjmark, Tillfors, Holländare, & Engström, 2015). While comparing the efficacy of relaxation training and cognitive-behavioural therapy for insomnia in patients with MDD, Norell-Clarke and colleagues (2015) reported that the latter was associated with shorter sleep onset latency, less middle insomnia, and improved function. However, both treatments had equal improvements in sleep quality, early morning awakening and total sleep time which may suggest that the type of sleep disturbance may impact function differently (Norell-Clarke et al., 2015).

Although the exact mechanisms are unclear, the importance of sleep on brain development and activity may provide important information for its contribution towards adequate function. In a review by Brand and Kirov, they examined the impact of sleep disturbances on the changes in psychological, cognitive, neurochemical, and physiological processes in adolescent populations (Brand & Kirov, 2011). Lack of sleep quality was associated with shortened latency to REM sleep, increased REM sleep amount, and insomnia, which consequently increased risk of depression, as well as impaired emotional regulation and

executive, cognitive and social function (Brand & Kirov, 2011).

Fatigue and Low Energy

While fatigue is closely related to sleep disturbances and may occur as a result of them, it is important to consider them as separate symptoms which may impact function differently. In a study by Xiao and colleagues, fatigue was more strongly associated with functional impairment in the occupational, social and family domains than sleep disturbances, despite the latter being more frequently reported in this sample (Xiao et al., 2018). Furthermore, in a study by Lam and colleagues (2012), approximately 39% of MDD patients attribute 'trouble sleeping at night' to impaired work ability, while 58% attribute it to 'low energy'.

Patients who demonstrate early improvements in fatigue after treatment often report larger improvements in function (Lam et al., 2017). There is also evidence that fatigue has disparate effects on the various domains of function. In a treatment study by Levada and Troyan (2019), they determined that baseline levels of fatigue were the most significant predictor of occupational function, whereas other symptoms had a greater association with social and family function. Interestingly, other evidence supports the specific effects of fatigue on occupational function, with some studies reporting that low energy had a greater impact on presenteeism (Lam et al., 2012). In contrast, some studies have reported that patients undergoing treatment report improved function alongside depressive symptoms, however, persistence of social impairments have been reported when fatigue continued to be present (McKnight & Kashdan, 2009). Other studies have observed that fatigue has an impact on the occupational, social and family domains, highlighting its general importance to functional impairment (Xiao et al., 2018).

To emphasize the importance of fatigue, Lam and colleagues determined that 58% of MDD patients reported that fatigue and low energy interfered with their ability to work, second only to low motivation at 59% (Lam et al., 2012). The current literature also suggests that higher levels of baseline fatigue have a significant association with reduced remission rates, and mental and physical function, which may be a result of its impact on motivation (Ferguson, Dennehy, Marangell, Martinez, & Wisniewski, 2014b; Nutt et al., 2007). Nutt and colleagues

suggest that high fatigue and lower energy levels are essential to driving adequate levels of motivation and effort to obtain rewards (Nutt et al., 2007). Notably, noradrenergic pathways influence symptoms related to fatigue, energy and hedonic responses and may be an important treatment target to improve in patients with reduced motivation (Blier, Gommoll, Chen, & Kramer, 2017; Lam et al., 2017; Nutt et al., 2007). Notably, serotonin-norepinephrine uptake inhibitors (SNRI) have yielded greater improvements in overall function than selective serotonin reuptake inhibitors (SNRI), which theoretically is driven by improvements in symptoms modulated by the noradrenergic system (Blier et al., 2017).

Motivation, Effort and Anhedonia

Symptoms associated with reduced positive affect, such as low pleasure, interest and fatigue, have been identified as key players in amotivation and reduced willingness to expend effort for rewards, which may impact social interactions and work performance (Nutt et al., 2007). Notably, motivation and effort are among the 'energy-consuming' facets of the reward response which may be linked to their impact on function (Rizvi, Pizzagalli, Sproule, & Kennedy, 2016). For example, in the STAR*D treatment study, 70% of patients with MDD continued to experience motivational deficits after treatment (Fervaha et al., 2016). These persistent motivational deficits accounted for 53% of the variance in functional impairment, independent of MDD severity and duration (Fervaha et al., 2016). Similarly, other studies have noted that improvements in motivation and interest had more robust impacts on improvements in function after treatment over other symptoms (Blier et al., 2017).

Importantly in a study by Lam and colleagues, they identified which depressive symptoms patients reported as having the most impact on their occupational function. Participants completed a questionnaire designed specifically for this study, which listed several depressive symptoms that could impact a patient's ability to work (Lam et al., 2012). The questionnaire asked participants to select how much a symptom impacted their ability to work on a 5-point Likert Scale. A symptom was defined as having clinically important interference on function if it was rated as "very much" or "so much that I had to stop working" on the questionnaire (Lam et al., 2012). A lack of motivation and energy were experienced in 93% and

96% of patients, respectively (Lam et al., 2012). More importantly, 59% and 58% of patients who experienced a lack of motivation and lack of energy, respectively, reported these symptoms had a clinically important interference on their ability to work, placing them at the top of the list (Lam et al., 2012). This result, combined with the high prevalence of these symptoms before and after treatment, suggests motivation significantly contributes to impaired function and requires additional attention.

Effort expenditure is often deficient in MDD due to altered cost-benefit analyses, which impact goal-driven behaviours and may subsequently impair function (Park, Lee, Kim, Kim, & Koo, 2017). Compared to healthy controls, patients with MDD overestimate the effort required to obtain rewards, have altered reward valuation and have disproportionate responses to positive and negative feedback (Park et al., 2017). Park and colleagues compared the differences in effort-based decision making and motivational levels between patients with MDD, patients with schizophrenia, and healthy controls (Park et al., 2017). Patients with MDD were more likely to anticipate and respond to negative reinforcement with high-effort and were unmotivated by low-effort positive reinforcement, whereas the opposite trend was found in patients with schizophrenia (Park et al., 2017). This suggests that the reward processing deficits impacting function may be distinct, warranting additional studies and targeted treatment regimens. With reward processing playing a significant role in functional impairment in MDD, more studies are needed.

Low motivation and effort are facets of anhedonia (Shelton & Tomarken, 2001), a cardinal symptom of MDD that reflects the loss of the ability to experience reward (Rizvi et al, 2016). Despite being a core symptom of MDD, few studies have directly studied the relationship between overall anhedonia and functional impairment, specifically occupational impairment. Studies analyzing the relationship between anhedonia and function are often secondary analyses and are scarce (Blier et al., 2017; Cao et al., 2019). Studies which have included anhedonia also commonly utilize scales which only measure consummatory pleasure or single items on depressive symptom scales, the latter of which is not psychometrically valid for the assessment of anhedonia (Blier et al., 2017; Levada & Troyan, 2019; Rizvi et al., 2015). For example, Cao and colleagues (2019) completed a *post-hoc* analysis of a primary study which

measured the sensitivity of a cognition screening tool (Cao et al., 2019). In this secondary analysis of a vortioxetine treatment trial for MDD, the outcome of interest was change in anhedonia, measured by the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) and the anhedonia items within the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery, & Asber, 1979), and general function was a secondary measure measured by the SDS (Cao et al., 2019). They reported that improvements in anhedonia after treatment, measured by changes in SHAPS score, strongly mediated the association between improvements in depressive symptoms and improvements in social function (Cao et al., 2019). More specifically, changes in anhedonia accounted for approximately 40% of this total variance (Cao et al., 2019). However, anhedonia was not found to significantly mediate the relationship between the other domains of function measured by the SDS and depressive symptom severity in this study (Cao et al. 2019).

In a pooled analysis of nine double-blind studies, Lam and colleagues (2017) evaluated the effect of the SNRI desvenlafaxine on energy and lassitude levels in MDD patients compared to placebo over an 8 week period (Lam et al., 2017). Furthermore, they explored whether baseline energy levels and early improvements in energy and lassitude were associated with functional and symptomatic outcome after treatment (Lam et al., 2017). The authors reported that early improvements in energy and lassitude strongly predicted early improvements in function and higher rates of functional remission (Lam et al., 2017). They noted that early improvements in function, measured by the SDS, were associated with higher combined remission rates of depressive symptoms and functional impairment (Lam et al., 2017). Finally, they observed that patients who continued to experience residual low energy and fatigue were more likely to continue experiencing functional impairment after 8 weeks of treatment (Lam et al., 2017). However, since anhedonia was measured utilizing items on the MADRS and not an anhedonia scale, conclusions regarding the specific effects of anhedonia on function cannot be established.

In a cross-sectional study, Rungpetchwong and colleagues (2017) reported that anhedonia significantly predicted overall functional impairment. However, their primary goal was to identify the level of distress associated with depressive symptoms, and how this

correlated with global function (Rungpetchwong et al., 2017). They utilized the 9-item Patient Health Questionnaire to measure several depressive symptoms, including anhedonia. While the original questionnaire has 9 questions, 3 questions were used to assess 6 symptoms for a total of 13 symptoms. This included different stages of insomnia, poor appetite versus overeating, and moving/speaking slowly versus restlessness (Rungepetchwong et al., 2017). However, this is typically not a standard method to measure these symptoms and may fail to fully capture important aspects of anhedonia (Rungpetchwong et al., 2017). The authors conclude that there was a strong correlation between anhedonia and functional impairment. However, the reported correlation coefficient was 0.40 (Rungpetchwong et al., 2017), which is considered a moderate correlation in the current literature (Akolgu, 2018) .

Currently, there are no studies which explore the neurobiological basis of functional impairment in MDD, specifically as it relates to anhedonia. However, other studies which have studied the neurobiological basis of reduced reward responsivity, particularly with respect to goal-driven behaviours, which may provide clues towards the relationship between anhedonia and functional impairment in MDD (Ferenczi et al., 2016; Levada & Troyan, 2019; Park et al., 2017; Rawal, Collishaw, Thapar, & Rice, 2013; Rothkirch, Tonn, Köhler, & Sterzer, 2017; Shelton & Tomarken, 2001; Slavich & Irwin, 2014). Generally, these studies reported that reduced willingness to expend effort and low levels of motivation were associated with impaired goal-driven behaviours important to function (Park et al., 2017). In addition, deficits in the connectivity of these reward-circuits responsible for goal-driven behaviours have been found to predict anhedonia (Ferenczi et al. 2016).

Given the preliminary evidence suggesting that reductions in anhedonia severity are associated with large improvements in function, it is crucial to understand this relationship more comprehensively. Despite being a core symptom of MDD, anhedonia has received disproportionally less attention in the context of function compared to other closely related symptoms, such as low motivation and effort expenditure, which have demonstrated significant contributions towards functional impairment. When studied, anhedonia is often relegated as a secondary outcome and utilizes tools that only assess consummatory pleasure, limiting a complete understanding of its association with function. Taken together, a direct analysis of the

complex relationship between anhedonia and functional impairment in MDD is required, which will be the focus of this thesis. By utilizing tools which reflect modern conceptualizations of anhedonia, greater insight into this relationship may be elucidated. However, to effectively understand the relationship between anhedonia and function, it is important to discuss our current understanding of anhedonia in MDD.

1.4 Anhedonia and Reward Processing

Content and Figures from Section 1.4 have been modified from the following:
Chow TK, Kennedy SH, Rizvi S. (2018). Anhedonia as a Crucial Factor of Depression: Assessment, Neurobiological Underpinnings and Treatment. In: Kim Yk. (eds) Understanding Depression. *Springer Nature, Singapore, 99-112.*

1.4.1 Anhedonia and Reward Processing in MDD

Anhedonia has received increased recognition due its prediction of MDD diagnosis, treatment response and remission (McMakin et al., 2012; Rawal, Collishaw, Thapar, & Rice, 2013; Uher et al. 2012.). Traditionally conceptualized as a "loss of pleasure", neuroscientific and behavioural evidence suggests that anhedonia is a more multi-faceted construct involving interest, anticipation, motivation, effort, expectation and consummatory pleasure (Chow, Kennedy, & Rizvi, 2018; RÃ¸mer Thomsen, Whybrow, & Kringelbach, 2015; Rizvi et al., 2016, 2015; Treadway & Zald, 2012). Thus, in the context of this thesis, anhedonia is defined as the clinical symptom presentation of these facets, and reward processing represents the underlying brain processes that yield reward-associated behaviours, which are commonly impaired in MDD and may impact function (Kiosses & Alexopoulos, 2005; Tam & Lam, 2012).

Reward processing models describe the facets of reward-seeking behaviour and their interactions. One conceptualization of reward processing is the Positive Valence System (PVS) from the Research Domain Criteria (RDoC), a National Institute of Mental Health framework for biomarker research in mental disorders (Insel et al., 2010). The goal of RDoC is to utilize a dimensional approach across "units of analysis", such as genes, brain circuits, and self-reports, to evaluate causes of mental illness rather than a single predictor in isolation (Hess et al. 2016; Vengeliene et al. 2017). The PVS is not a model of reward processing, per se, but a suggested

starting point for the constructs pertinent to a reward processing model which include the ability to make a reward-stimulus association, motivation, effort, expectation, and consummatory pleasure.

Another model by Rizvi and colleagues, has been put forth to depict the associations among these facets (**Figure 1**) (Rizvi et al., 2016). In this model, the reward process is described as initially requiring a stimulus-reward association, which then leads to interest, anticipation, motivation, effort, hedonic response, and feedback integration (Rizvi et al., 2016). After a reward-stimulus association has been established, an interest in the rewarding stimulus can then develop. Importantly, interest in reward is important to be able to anticipate it or to develop a "wanting" for a reward (Rizvi et al., 2016). The brain also needs to calculate the energy required to obtain the reward. Motivation describes the initial energy expenditure to obtain a reward and effort describes the sustained energy expenditure. In other words, motivation is required to start the process of reward obtainment and effort is required to continue this process. Outcome following reward can be negative, positive (pleasurable) or neutral. Consummatory pleasure describes the pleasure experienced by an individual as they directly interact with the stimulus "in the moment". Using outcome from previous stimulus-reward associations, individuals develop expectations of reward. These expectations may relate to whether a reward will be present, the likelihood of attainment, and magnitude of experienced pleasure or the effort required to obtain it. Reward expectations may influence other facets of reward such as the level of anticipation experienced or motivation to attain a reward (Rizvi et al., 2016). Expectation can also affect the original stimulus-reward association through feedback integration, which is the ability to utilize new information to update existing knowledge of a potential reward. This reward learning ability is crucial to maintain accurate expectations and associations of the stimuli for future encounters. For example, there may be only certain contexts where a stimulus is rewarding, or a stimulus may no longer be rewarding at all. In addition, the value one places on a stimulus can vary considerably by several factors including the time to attainment and the magnitude of the reward. It is important to note that, while reward processing is depicted as a linear process in **Figure 1**, the facets may act in parallel. MDD patients demonstrate deficits across these facets (reviewed in Rizvi et al. 2016;

Treadway and Zald 2012; Tremblay et al. 2005), although the specific factors and conditions that contribute to these deficits need further exploration.

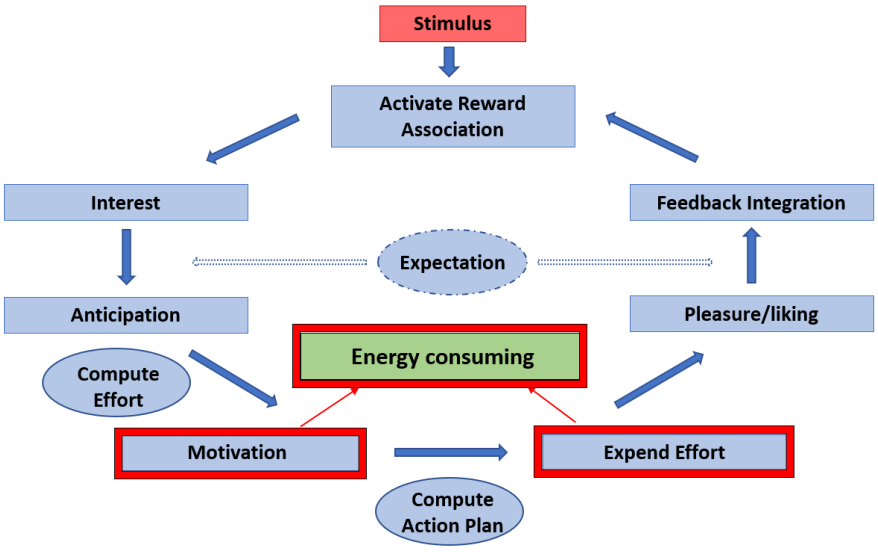


Figure 1. Model of Reward Processing by Rizvi and colleagues (2016). The energy consuming facets (motivation and effort) have been highlighted in red.

1.4.2 Measurement of Anhedonia

Currently, anhedonia is measured via self-report scales and behavioural tasks. While both tools allow for the assessment of anhedonia, each provides a unique, but equally important perspective on this core symptom. In line with this, Treadway and Zald (2011) strongly propose that both should be used in tandem to obtain a more complete understanding of anhedonia (Treadway & Zald, 2011).

MDD patients often display reduced interest in rewarding stimuli (Uher et al., 2008; Uher et al. 2012), therefore, self-report scales are particularly useful since they can directly assess anhedonic symptoms (Kringelbach et al. 2012; Rizvi et al. 2016). The measurement of the explicit facets of anhedonia are particularly important due to the subjective nature of reward behavior (reviewed in Chow et al., 2018; Rizvi, 2014; Rizvi et al., 2016). Furthermore, specific activities that are perceived as rewarding vary between each person. Therefore, self-report scales should ideally be generalizable across cultures and individuals. However, many current scales, including the current gold standard (i.e. SHAPS), are limited to measuring aspects of

consummatory pleasure (Rizvi et al., 2016). With the increased focus on expanding the construct of anhedonia beyond consummatory pleasure, there have been recent developments of anhedonia scales to reflect these changes and to address these limitations, including the Dimensional Anhedonia Rating Scale (DARS) (Rizvi et al, 2015).

Self-report scales provide direct insight into experiences of anhedonia and have demonstrated important utility in clinical settings; however, they possess several limitations. While many consider rewarding experiences and its associated pleasures, motivations, interests, and anticipation, an entirely conscious experience, this may not be the case (Kringelbach et al., 2012). Several lines of evidence suggest that these experiences, while often conscious, may include an unconscious component. Kringelbach (2012) asserts that at times we may be poor introspecting on our current emotional states. Further, he suggests that this may lead to a reduced awareness of what motivates us, what interests us or what brings us pleasure (Kringelbach et al., 2012). Several studies have suggested that reward learning often occurs implicitly. A study by Pessiglione and colleagues (2008) utilized a behavioural task which presented healthy participants with two cues, one associated with a monetary reward and another associated with a "punishment" (Pessiglione et al., 2008). As the task progressed, participants were more prone to selecting the cues associated with a reward without their awareness, supporting the presence of implicit reward processing (Pessiglione et al., 2008). Where self-reports can provide great explicit information, behavioural tasks can tap into both the conscious and unconscious, and as such are valuable objective measures in the study of anhedonia.

1.4.3 Neurobiology of Anhedonia and Reward

The nucleus accumbens (NAc) has long been acknowledged as the "pleasure centre" of the brain and has historically been tied to anhedonia (Wong et al. 1991). However, we now have a deeper understanding of the role of other brain regions in reward processing, which include the prefrontal cortex (PFC), amgydala, dorsal and ventral striatum and the insula (reviewed in Der-Avakian & Markou, 2012; Treadway, 2015). Indeed, Whitton et al. (2015) reported that separate neurobiological pathways may partially govern the activity of each

reward facet, supporting the idea of distinct and overlapping neurocircuitry across reward facets. For example, the PFC is involved in higher cognitive processing of reward, including reward valuation, decision making, context integration and cost-benefit analysis (Elliot et al. 2000, Grabenhorst and Rolls 2011). The oribitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC) are particularly involved in these processes (reviewed in Treadway, 2015). In addition, evidence suggests that once a stimulus has been identified as pleasurable, the anterior cingulate cortex (ACC) is a brain region involved in cost-benefit analysis and effort-related functions required to obtain reward (Salamone et al., 2009, Treadway & Zald, 2011, reviewed in Der-Avakian & Markou, 2012). Using this information, the vmPFC may be responsible for executing the decision to carry out reward-directed behaviours (Grabenhorst & Rolls, 2011). Furthermore, the vmPFC, ACC, OFC and striatum may also be involved in reward processing by monitoring the rewarding properties of a stimuli (Elliot et al. 2000, Seo & Lee, 2007).

Deficits in the neurobiological underpinnings of reward processing have been found to correlate with the clinical symptom of anhedonia in some studies (reviewed in Rizvi et al., 2016). Notably, reduced “reward responsivity”, defined according to the reward sensitivity subscale on the Behavioural Activation Scale (Carver, & White, 1994), was associated with hypoconnectivity between the nucleus accumbens and the default-mode network (DMN) across mood disorders (Sharma et al., 2017). The DMN is active during rest and is thought to play a role in self-reflection, including the integration of memories and other important information, such as personal goals and motivations (Buckner et al., 2008). The specific regions of the DMN with diminished connections to the nucleus accumbens include the anterior and dorsal PFC and the posterior cingulate cortex (PCC) (Sharma et al. 2017). In contrast, reduced reward responsivity was associated with hyperconnectivity between the nucleus accumbens and the cingulo-opercular network, in particular with the insular cortex (Sharma et al. 2017). While the role of the insula in reward is unclear, some evidence has suggested that it is involved in the effort to acquire rewards (Prevost et al., 2010; Treadway, 2015). Interestingly, imaging studies have suggested that decreased insula activation, as a result of decreased dopamine release, may be associated with the selection of high effort reward options (Prevost et al.,

2010; Treadway 2015). When it comes to effort, evidence has suggested that the insula and striatum are involved in antagonistic roles (Prevost et al., 2010, Treadway 2015). High levels of effort expenditure is associated with low insula activation and high striatum activation, with low and high levels of dopamine activity respectively (Prevost et al., 2010, Treadway 2015). It is possible that a neural dysfunction in any part of the reward processing circuit could lead to the clinical symptom of anhedonia and subsequent functional impairment, but this remains to be empirically validated.

With respect to neurotransmission in reward processing, reduced levels of dopamine have been demonstrated in MDD, which affect pleasure and goal-driven behaviour and may have negative impacts on function (Nutt et al., 2007, Malhi et al. 2007; Salamone et al. 2003). In depressed individuals, reduced dopamine levels have been found in the ACC, nucleus accumbens putamen, ventral striatum, PFC and OFC (Park et al., 2017). Increased medial PFC activity in MDD may attenuate striatal activity, subsequently reducing behaviour associated with dopaminergic stimulation, such as goal-driven behaviour (Ferenczi et al., 2016). Consequently, goal-driven behaviours related to motivation may be reduced, thereby impairing function. Exposure to pleasant stimuli increases dopamine activity in the ventral striatum; however, this dopamine activity can be reduced in MDD patients (Schultz, 1998). Interestingly, this reduced dopamine activity in the ventral striatum is correlated with anhedonia severity, but not necessarily depressive symptom severity (Treadway, 2015). However, preclinical findings have helped to elucidate the role of dopamine as being more linked to anticipation and motivation rather than pleasure (Salamone et al., 2003; Schultz, 1998). Treadway (2015) reported that dopamine activity in the insula and ventral striatum had different effects on effort-based decision-making. Increased dopamine activity in the ventral striatum was correlated with increased effort in a dose-dependent manner; however, the opposite trend was observed in the insula (Treadway, 2015). Importantly, studies indicate that dopamine does not act in isolation and that serotonin, GABA, glutamate, and opioids may play an important role in reward (McCabe et al. 2010, Wassum et al. 2009, Wong et al. 1991). For example, in MDD lower serotonin levels contribute to several symptoms including somatic anxiety and low mood, which may all impact function (Shelton & Tomarken, 2001). While serotonin plays a significant

role in MDD, selective serotonin-reuptake inhibitors (SSRIs) may not adequately treat symptoms related to low pleasure, energy, and interest, all of which are related to function (Nutt et al., 2007). However, noradrenergic pathways are implicated in playing a role in function. Reduced activity in this system among those with MDD is associated with amotivation, low positive affect, mental and physical slowing, and energy levels (Shelton & Tomarken, 2001). Patients with these symptoms have demonstrated greater success with functional recovery when treated with norepinephrine reuptake inhibitors (Blier et al., 2017). Reduced levels of norepinephrine may be a plausible contributor to the high prevalence of low energy and amotivation as residual symptoms, subsequently resulting in lingering dysfunction (Kennedy et al., 2019).

1.5 Resting-State Functional Magnetic Resonance Imaging

1.5.1 Overview of resting state fMRI

Recent advances in functional magnetic resonance imaging (fMRI), particularly the quality, speed and safety of imaging, have promoted its use in MDD research to explore abnormalities in brain activity. Through the manipulation of several magnetic fields, fMRI can measure changes in blood-oxygen-level dependent (BOLD) signals as a proxy of brain activity (Beckmann et al., 2009; Logothetis, & Wandell, 2004a). This allows for a non-invasive method to visualize functional connectivity in the brain. Currently, fMRI is either utilized in conjunction with a behavioural task, known as task-based fMRI, or in the absence of activity, known as resting-state fMRI (rsFMRI). Task-based fMRI provides insight into changes in brain activity between regions that may be associated with completing a specific behaviour (Joel et al., 2011; Zhang et al., 2016). In the context of MDD, utilization of task-based fMRI has seen a recent increase to assess cognitive functions, such as psychomotor speed, and reward responsivity (Guo et al., 2015; Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014; Mansur et al., 2019; Sternat & Katzman, 2016). In contrast, rsfMRI is utilized to explore networks in the brain which may connect regions functionally (Zhang et al., 2016). At rest, the brain continues to remain highly active, specifically in certain networks. Functional connectivity can be described as either

within-network or between network activity, therefore rsfMRI may provide insight into the organization of intrinsic brain activity (Joel et al., 2011). Given current evidence that the functional connectivity at rest resembles the activity during the completion of a task, rsfMRI may be a useful tool to study the functional networks of the brain and how they may be associated with various symptoms of MDD (Cole et al., 2014).

1.5.2 Seed-Based vs Independent Components Analysis

Currently, there are two primary approaches to analyzing rsfMRI data: seed-based correlational analysis and independent component analysis (ICA). Seed-based approaches require an *a priori* selection of a region of interest (ROI) and utilize its mean time course of activity as a regressor in a general linear model. The ROI can be a group of voxels selected in accordance with results of a previous study, or voxels associated with a brain region in reference to an atlas (Wu et al., 2018). The time course of activity for the whole brain is then assessed relative to this ROI. Regions with greater correlation in activity with the ROI over the same time-course are thought to be functionally connected. This allows for the visualization of a network which has functional connectivity with the specified ROI (Cole et al., 2014). Seed-based analyses have the advantage of being more simplistic in nature, requiring less computational power and are adequate for smaller sample sizes (Cole et al., 2014; Wu et al., 2018). However, since this is a hypothesis-driven approach, the validity and reliability of the results are dependent on a sound theory (Wu et al., 2018). Furthermore, since this method only assesses the functional connectivity of the brain relative to this ROI, it will not capture any other functional networks in the rest of the brain (Guo et al, 2015; Wu et al., 2018).

ICA is a data-driven, exploratory approach to studying functional connectivity of the whole brain. By analyzing the activity of the all the voxels of the brain, ICA separates rsfMRI data into individual components according to their spatial and temporal relationships (Beckmann & Smith, 2004). These components may involve motion artifacts or physiological processes which can be removed. However, the components are obtained by maximizing statistical independence between each other, which may be more difficult to interpret than seed-based approaches (Wu et al., 2018). Furthermore, this may result in the separation of

networks into separate components. However, its real usefulness lies in the identification of potential functional networks throughout the entirety of the brain, allowing for more exploratory analyses that can inform future studies (Beckmann, & Smith, 2004).

1.5.3 Resting State Networks in MDD associated with Function

The study of the underlying resting state functional connectivity associated with functional impairment in MDD is in its infancy. While studies have observed the differences in brain activity associated with contributors of functional impairment, such as cognitive deficits, to our knowledge there are no published studies that directly assess the relationship between function and resting state networks in MDD. However, there are common functional networks which have been implicated to play a role in MDD that may provide insight into their potential effects on functional impairment.

Networks involved with motivation, interest, introspection of goals, and emotional regulation, such as the default mode network (DMN), salience network (SN), and ventromedial network (VMN) may have importance in function (Fresco et al., 2017; Nishimura et al., 2015). The DMN consists of the PCC, precuneus, vmPFC and parietal lobe, which can be further separated into an anterior and posterior subnetwork. The DMN is most active during rest and inactive during goal-driven activity, specifically in the PFC (Ikeda, Shiozaki, Ikeda, Suzuki, & Hirayasu, 2013; Scult et al., 2019). This network has been implicated in playing a role in self-referential cognitive processes, and receives input from other brain regions, such as the vmPFC, while reflecting on goals (Alexopoulos et al., 2012; Brzezicka, 2013; Sharma et al., 2017). Greater within-network activity of the posterior, ventral and core DMN subsystems has been observed in MDD (Sambataro, Wolf, Pennuto, Vasic, & Wolf, 2014). In one study by Kumar et al. they determined that MDD patients had greater activation in areas associated with the DMN, such as the amygdala, insula, and ventrolateral prefrontal cortex, in response to social exclusion (Kumar et al., 2017). This activity correlated negatively with hedonic tone and self-esteem which the authors propose are risk factors for interpersonal stress and impaired social function (Kumar et al., 2017).

The SN is an executive control network that has a role in task-switching, evaluating and

integrating information associated with salient stimuli and modulating the activity of other networks (Gradin et al., 2011; Steffens, Wang, & Pearlson, 2019). More specifically, after filtering salient stimuli, the SN coordinates other networks to initiate behaviours driven by motivation in response to important stimuli (Menon, 2011; Seely et al., 2007). The SN includes brain areas involved with emotional processing, motivation and goal-driven behaviour, and executive function (Seely et al., 2007; Yeo et al., 2011). This includes areas such as the ACC, dlPFC, dorsal striatum, limbic regions, putamen, and anterior insula. Increased connectivity between these regions has been associated with increased with response times towards salient stimuli (Seely et al., 2007). Altered connectivity between these brain regions have been implicated in impaired goal-driven activity and emotional regulation, which may act as a link between anhedonia and function.

The VMN is associated with what many know as the traditional reward pathways. The VMN shares many brain regions associated with the SN such as the ACC, but also the vmPFC, ventral striatum and ventral tegmental area (Chin Fatt et al., 2019; Kerestes et al., 2014). Given that many of these brain regions are associated with dopaminergic pathways, the VMN plays a key role in reward processing (Sternat & Katzman, 2016). The VMN is responsible for evaluating whether a stimulus is positively or negatively valanced and also drives goal-driven behaviour (Arana et al., 2003), and so may contribute to functional impairment in MDD.

Chapter 2

Study Objectives and Hypotheses

2.1 Identified Needs

Functional impairment in MDD is caused by a myriad of contributors and is associated with significant economic burden, largely driven by impairment in occupational function (Lam et al., 2012, 2016). Since current treatment regimens, remission criteria and research primarily focus on depressive symptoms, the persistence of functional impairment in MDD remains understudied as a treatment target with respect to understanding its key contributors. Patients with MDD commonly attribute low energy, motivation levels and willingness to expend effort as primary contributors to their reduced ability to work (Lam et al., 2012). Importantly, motivation and effort are facets of anhedonia, a core symptom of MDD (Blier et al., 2017; Lam et al., 2017). Preliminary evidence has suggested that reductions in the severity of anhedonia is associated with improvement in function among patients with MDD (Cao et al., 2019). Importantly, the anhedonia measures in these studies either include single items from depressive symptom scales or scales which solely measure consummatory pleasure (Cao et al., 2019; Rungpetchwong et al., 2017), which limits conclusions of the association between anhedonia and function. Given these data and the fact that anhedonia is a core symptom of MDD there is a strong rationale to understand its relationship more comprehensively with functional impairment by studying it at a clinical, behavioural, and neurobiological level.

Clinically, few studies have directly studied the association between anhedonia severity and impairment in occupational function in MDD, and often study function as a secondary outcome. Preliminary evidence has suggested that deficits in the facets of anhedonia are associated with greater functional impairment in patients with MDD. Several studies report that motivational deficits and reduced effort expenditure, based on self-report scales, are strongly associated with impairment in occupational function (Fervaha et al., 2016; Lam et al., 2016, 2017; Nutt et al., 2007). Importantly, current evidence demonstrates that motivational deficits

often persist after treatment and account for significant variance in functional impairment (Fervaha et al., 2016). In addition, antidepressant treatments which improve motivation, energy and effort have demonstrated greater efficacy in the improvement of function, specifically in the occupation domain. However, despite these findings, it remains unclear how anhedonia severity impacts occupational function in MDD, limiting a comprehensive understanding of this relationship.

Behaviorally, patients with MDD often demonstrate lower motivation and effort levels when completing behavioural reward-tasks (Park et al., 2017). Impaired cost-benefit decision-making has also been observed, which can include an overestimation of the effort required to obtain rewards (Park et al., 2017). This has been interpreted as increased amotivation and lack of drive to obtain rewards in MDD. Ultimately, there is a reduction of goal-driven behaviours that may, subsequently, have an important impact on functioning in patients with MDD (Fervaha et al., 2016; Park et al., 2017). However, there are currently no studies which directly link reward-tasks with functional impairment in MDD.

Neurobiologically, there are no studies assessing the underlying neuroactivity of functional impairment, especially with rsfMRI. However, evidence suggests that altered functional connectivity in MDD has been associated with reduced goal-driven behaviours, driven by impaired motivation and effort-expenditure. Since these behaviours are implicated for optimal function, it is reasonable to hypothesize that functional impairment and anhedonia may manifest as disruptions in brain connectivity underlying reward networks.

There are several important clinical implications gained by understanding the relationship between anhedonia and impairment in occupational function in MDD. Obtaining a more fulsome measurement of anhedonia as it relates to function provides a rationale to explore anhedonia as a potential treatment target to alleviate functional impairment in MDD. Therefore, to advance our current understanding of occupational function, the following needs have been identified:

1. Determine how impairment in occupational function is affected by anhedonia in MDD measured by self-reports.

2. Refine the relationship between behavioural presentations of reduced reward responsivity; specifically, task-based effort-expenditure and incentive motivation, and their potential links to impairment in occupational functioning in MDD.

3. Directly explore the resting-state functional connectivity patterns, specifically in the DMN and SN, which may be associated with impairment in occupational function and anhedonia in MDD.

2.2 Objectives and Hypotheses

The overarching aim of this study was to gain a more comprehensive understanding of the interaction between occupational function and anhedonia in MDD by assessing this association at a clinical, behavioural, and neurobiological level. The primary objective was to determine the association between occupational function and anhedonia in MDD measured through self-reports. Secondary objectives aimed to supplement the primary objective by assessing the relationship between impairment in occupational function with behavioural tasks of reward processing and brain reward system connectivity. The specific objectives and hypotheses are indicated below.

Objective 1:

To determine whether impairment in occupational function in MDD, measured via the Lam Employment Absence and Productivity Scale (LEAPS), is associated with subjective reports of anhedonia, primarily using the DARS.

Primary Hypothesis:

Impairment in occupational function in MDD will be associated with higher levels of anhedonia, indicated by a negative correlation between the LEAPS (total score and all subscale scores) and DARS scores (total score and all subscale scores). Impairments in occupational function will be

related to anhedonia levels in a negative, linear fashion, where higher scores on the DARS will predict lower scores on the LEAPS.

Secondary Hypotheses:

(1) Impairment in occupational function in MDD will be associated with higher levels of anhedonia, indicated by a positive correlation between the LEAPS (total score and all subscale scores) and SHAPS score. Impairments in occupational function will be related to anhedonia levels in a positive, linear fashion, where higher scores on the SHAPS will predict higher scores on the LEAPS; (2) Compared to healthy controls, participants with MDD will display greater levels of impairment in occupational function (measured by the LEAPS), and anhedonia (measured by the DARS and SHAPS).

Objective 2:

To determine the extent to which occupational function in MDD are associated with incentive motivation and effort-expenditure, measured through the Cued Reinforcement Reaction-Time Task (CRRT) and Effort-Expenditure for Reward Task (EEfRT) respectively.

Hypotheses

(1) Higher levels of impairment in occupational function will be associated with poor performance on the CRRT, measured by reinforcement-related speeding (indicative of the degree of wanting or incentive motivation); (2) Participants with MDD will demonstrate lower reinforcement-related speeding than healthy controls, with lower magnitudes indicative of lower reinforcement-related speeding; (3) Higher levels of impairment in occupational function will be correlated with reduced willingness to expend effort for reward, indicated by a lower proportion of hard tasks chosen relative to the easy tasks on the EEfRT (4) Higher levels of occupational impairment will be associated with decreased selection of the hard task, measured via generalized estimating equation models, after controlling for reward magnitude, probability and expected value (5) Participants with MDD will be less willing to expend effort

than healthy controls, thus will be less likely to select the hard task at each probability level.

Objective 3:

To determine whether levels of impairment in occupational function in MDD, measured by the total LEAPS score, and anhedonia, measured by the total DARS score, are associated with resting state functional connectivity, specifically in the default-mode network and salience networks, and to identify whether these same networks differ in resting state activity with healthy controls.

Hypotheses:

(1) Resting state connectivity in the default mode network and salience network, will positively correlate and negatively correlate with levels of occupational functioning impairment and anhedonia, respectively; (2) Resting state connectivity in the DMN and SN, will positively correlate and negatively correlate, respectively, with levels of anhedonia (3) Resting state connectivity in the default-mode network and salience networks will differ between participants with MDD and healthy controls, with higher activity in the DMN and lower activity in the SN among participants with MDD.

Chapter 3

Research Design and Methods

3.1 Design

The purpose of this cross-sectional study was to identify an association between anhedonia, measured through self-reports, reward-based behavioural tasks and rsfMRI, and impairment in occupational function in MDD. This specific study was embedded into an open-label, fixed dose 8-week clinical treatment trial of desvenlafaxine in previously unmedicated participants with MDD compared with healthy controls. The focus of the present study was data collection on anhedonia and function at the baseline visit of the clinical trial, prior to the administration of desvenlafaxine.

3.2 Subject Selection

3.2.1 Recruitment

All participants were recruited either via self-referrals or physician-referrals at the Department of Psychiatry at St. Michael's Hospital (SMH). Participant flyers and study information brochures were disseminated at SMH, SMH-associated family clinics, consenting family clinics in the downtown Toronto area, the University of Toronto, Ryerson University, and hospitals part of the University Health Network (UHN). Participants also found information online through the Arthur Sommer Rotenberg Suicide and Depression Studies website or the ClinicalTrials.gov database. Past participants from closely associated studies who have provided consent to be contacted about other studies were also recruited. The protocol of this study was approved by the Research Ethics Board at SMH, UHN, the University of Toronto and Ryerson University. All participants provided written informed consent prior to conducting research activities at the screening visit conducted at SMH.

3.2.2 Participants with Major Depressive Disorder

Inclusion Criteria

1. Ages between 18 and 60 years
2. Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V) (American Psychiatric Association, 2013) criteria for a current MDE, confirmed through the MINI Neuropsychiatric Interview (MINI) (Sheehan et al., 1997).
3. Hamilton Depression Rating Scale – 17 item (HAMD-17) (Hamilton, 1960) score of $\geq$ 17 (moderate to severe symptoms)
4. Free of psychotropic medications for $\geq$ 5 half-lives before the study visit
5. Ability to undergo MRI scanning (absence of metal, pacemakers, etc.)

Exclusion Criteria*

1. Pregnancy or lactation
2. Medical condition requiring immediate investigation or treatment
3. Recent ($\leq$ 6 months) or current history of drug abuse/dependence, including ethanol (other than caffeine, or nicotine)
4. Lifetime history of psychosis, other Axis I comorbidities are allowable
5. Significant Axis II diagnosis (e.g. Borderline Personality Disorder)

*Since this thesis project was part of a larger treatment study evaluating the effects of desvenlafaxine on reward processing and function, there were additional exclusion criteria for participants with MDD including: previous intolerance of failure to respond to an adequate trial of desvenlafaxine, failure of > 2 antidepressant treatments of adequate dose and duration for current MDE, and medical contraindications of desvenlafaxine (uncontrolled hypertension, cardiovascular or cerebrovascular conditions, seizure disorders, osteoporosis, etc.)

3.2.3 Healthy Controls

Inclusion Criteria

1. Ages between 18 and 60 years
2. Ability to undergo MRI scanning (absence of metal, pacemakers, etc.)

Exclusion Criteria

1. Pregnancy or lactation
2. Medical condition requiring immediate investigation or treatment
3. Lifetime history of any psychiatric disorder
4. Lifetime history of receiving an antidepressant

3.3 Procedure

3.3.1 Screening

All potential participants were screened to confirm study eligibility. An initial telephone interview was performed as a pre-screen to exclude individuals who did not meet essential eligibility criteria, including proper diagnoses, and the ability to undergo MRI scanning. Individuals who were identified as potential candidates attended an in-person screening visit to confirm eligibility.

During the screening visit, all contents of the informed consent form, including the assessments, study structure, and risks were discussed, and any outstanding questions were answered. Participants signed the form in the presence of the study coordinator before proceeding with any screening assessments. Afterwards, the study coordinator administered the MINI structured diagnostic assessment to ensure each participant group met the appropriate psychiatric diagnostic inclusion criteria (Sheehan et al., 1997). This was followed by a consultation by a study psychiatrist who confirmed the participant's diagnoses and that their depression severity met criteria based on the HAMD-17 (Hamilton, 1960). The study psychiatrist further assessed the participant's medical and physical history. Demographic information such as age, gender, occupation, marital status, and education were collected to

ensure healthy controls were age and sex-matched with participants with MDD for imaging purposes. Medication history and any current adverse effects experienced by the participant were also collected. Urine and blood samples were collected at the outpatient blood lab at SMH for standardized drug toxicology screening.

Participants with MDD receiving antidepressants that were determined to be ineffective by the study psychiatrist were tapered off of their medication and were unmedicated at least 5 half lives prior to the baseline visit. Participants unable to complete the study visit within 42 days of the screening visit were re-screened to reconfirm eligibility. Participants with confirmed eligibility continued with the study.

3.3.2 Study Visit

The study coordinator confirmed whether participants continued to meet eligibility criteria. This was followed by a consultation with the study psychiatrist who administered the HAMD-17 to confirm depression severity. Subsequently, participants completed self-report questionnaires which assessed their occupational function and anhedonia. All self-report measures were completed in the presence of the study coordinator. After completion of the self-reports, the participants completed computerized behavioural reward tasks, which were administered in a randomized order. These tasks were designed to isolate and probe motivation and effort.

Following self-report and behavioural task completion, participants underwent an MRI scan. Prior to the MRI scan, the study coordinator ensured that participants removed all metal objects such as jewellery, metal-wired bras, belts, and glasses. The study coordinator was present for the entire duration of the MRI scan.

3.4 Measures

Functional impairment and anhedonia were assessed with several self-report scales and behavioural tasks. Depression severity was evaluated via a clinician-administered scale. Primary outcome measures are denoted with an asterisk.

Function Measure

Lam Employment Absence and Productivity Scale (LEAPS)*

A 10-item self-report scale used to assess aspects of occupational function including productivity and absenteeism (Lam et al., 2009). The LEAPS was designed for use and validated specifically in populations with MDD. Participants are asked to fill in their current occupation, the number of hours expected to work, and the number of hours missed from work. Participants are then asked to rate how frequently certain factors impacted their ability to work over the past two weeks, including low motivation and effort. The last three items on the LEAPS encompass a 'productivity subscale', which is indicative of an individual's level of presenteeism. The percentage of the hours missed relative to the hours expected to work was utilized as a measure of absenteeism. Higher scores on the LEAPS is indicative of greater impairment in occupational function. Functional impairment measured by the LEAPS is correlated with the SDS, the current gold standard for assessing function (Lam et al., 2009, Leon et al., 1997).

Anhedonia Severity

Dimensional Anhedonia Rating Scale (DARS)*

The Dimensional Anhedonia Rating Scale (DARS) is a validated 17-item scale that measures interest, motivation, effort and consummatory pleasure (Rizvi et al., 2015). Participants are asked to fill in personal activities or experiences they perceive as enjoyable across the domains of hobbies, social activities, food/drink, and sensory experiences. Low score represents greater anhedonia.

Snaith Hamilton Pleasure Scale (SHAPS)

The Snaith-Hamilton Pleasure Scale (SHAPS) is a 14-item scale designed to assess hedonic capacity and is the current gold standard of anhedonia measurement in research on MDD (Snaith et al. 1995). Higher scores are indicative of greater levels of anhedonia.

Behavioural Reward Tasks

Effort Expenditure for Reward Task (EEfRT)

The EEfRT task studies a subject's effort-based decision making by manipulating the win probability and magnitude of the reward options (Treadway et al., 2009). The task is composed of several trials where participants are tasked to repeatedly press a single button a set number of times within a time limit to obtain a monetary reward. In each trial, participants are given an option to select between a "easy" and "hard" version of the task, also known as the "low cost, low reward (LC/LR)" and "high cost, high reward (HC/HR)" options, respectively. The easy trials required the subjects to repeatedly press a button 30 times in 15 seconds with their dominant index finger. In contrast, the hard trials required the subjects to repeatedly press a button 100 times within 21 seconds using their non-dominant pinky finger. The easy and hard options of the task have an associated win probability and reward with a monetary value. Successful completion of the task was associated with a chance of acquiring a reward of a certain value: the easy trials have a fixed monetary gain of $1.00 whereas the hard trials may reward between $1.24 to $4.30. For the hard trials, rewards under $2.31, between $2.31 to $3.29 and greater than $3.29 were coded as low, medium, and high reward magnitudes, respectively. The probability of obtaining the reward also varies between the options of 12%, 50%, and 88%, designated as low, medium, and high, respectively. An example of a single trial can be seen in **Figure 2**. The win probability and magnitude associated with each task type is explicitly presented to the participant before they make their decision. Whether they will obtain the reward in this task is pre-determined and unbeknownst to the participant. As a result, the task encourages subjects to make the optimal decision to obtain the largest monetary total, allowing us insight into their decision-making process. This version of the task was completed in the software OpenSesame version 2.9.7 (Mathôt, Schreij, & Theeuwes, 2012).

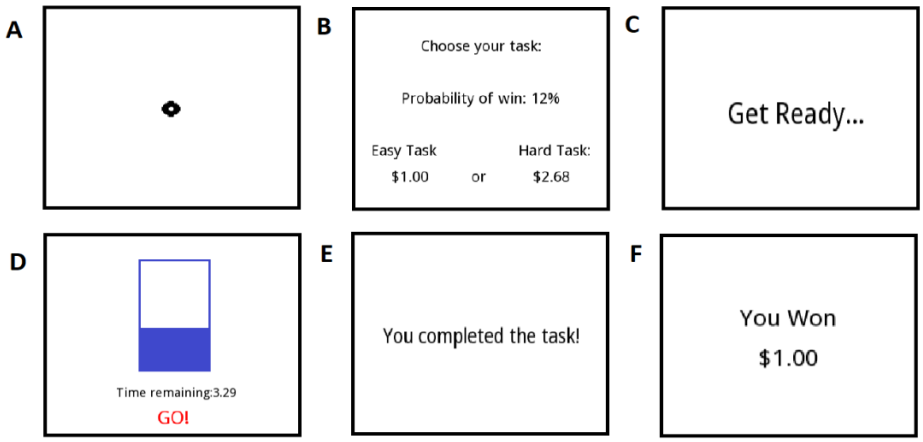


Figure 2. An example of a single trial for the Effort Expenditure for Reward Task. A) Fixation cue (1 s) B) Participants are given the reward probability and reward magnitude and are asked to select either the Easy or Hard task (5 s) C) Ready screen (1 s) D) Task screen where participants are asked to repeatedly press a single button (Easy task = 7 s; Hard task = 21 s) E) Completion feedback F) Feedback on whether task was rewarded

Cued-Reinforcement Reaction Time Task (CRRT)

The CRRT task analyzes an individual's level of incentive motivation through the utilization of their reward-based reaction time (Cools et al., 2005). The task is composed of a practice phase and main testing phase where subjects are presented with 3 circles and are instructed to choose the 'odd-one-out'. The practice phase consists of two blocks, where subjects are instructed to complete each trial as fast as possible while minimizing mistakes. The purpose of the first block is to familiarize subjects with the task and the second block is utilized to obtain the subject's mean reaction time cut-offs and standard deviations for the main testing phase. These individual cut-offs for each subject allow the mitigation of some of the confounding effects, such as age, on reaction time. The main testing phase is composed of two versions (1 and 2) with a pair of phases (a and b) in each version. Participants completed one version of the task, selected by a randomizer. Although the primary goal of the main phase remains the same as the practice blocks, there are several differences. First, the subjects are instructed that not all trials will award points and that this will be predetermined according to a coloured frame around the circles. The colours of the frames are red, blue or yellow and the probability of obtaining reinforcement is 10%, 50%, or 90% respectively. Furthermore, the number of points awarded varied according to the reaction time of the participant: fast and

correct responses were awarded 100 points, correct but slow responses were awarded 1 point and incorrect responses award 0 points. Feedback for correct answers were represented visually using a green smiley face and incorrect responses with a red sad face. Furthermore, these responses were also associated with an audio cue: fast and correct responses were associated with a 'flourish' sound, slow and correct responses were associated with high-frequency tone and incorrect responses with a low-frequency tone. Participants are encouraged to obtain as many points as possible. A single trial and potential outcomes can be seen in **Figure 3**. The main outcome of interest is reinforcement-related speeding (CRRT-RRS) which is representative of the degree an individual modulates their behaviour in response to reward cues. CRRT-RRS is calculated by obtaining the difference between the mean reaction time for low probability trials and the mean reaction time for high probability trials. Higher magnitudes of CRRT-RRS is indicative of higher levels of incentive motivation. This version of the task was coded in Visual Basic. After completion of the task, subjects completed a debrief questionnaire which addresses whether they were aware of the colour contingencies.

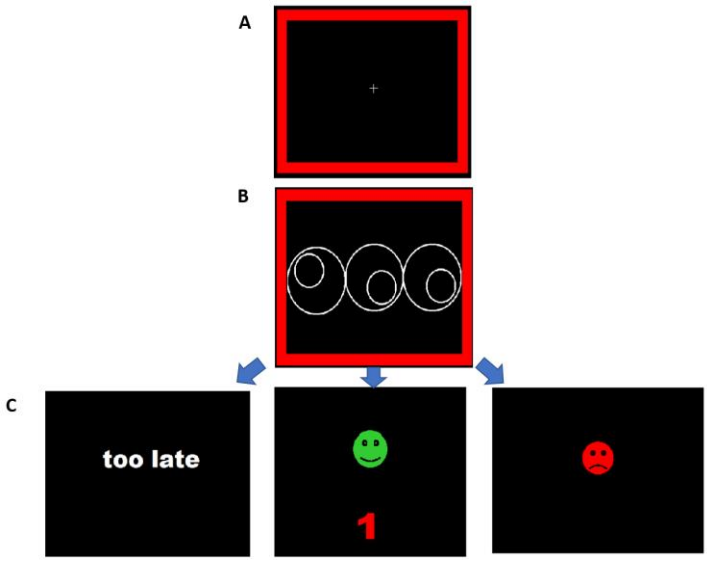


Figure 3. An example of a single trial and potential outcomes for the Cued Reinforcement Reaction-Time Task. A) Fixation cue B) Task screen where participants are asked to select the 'Odd-one-out'. Reward contigency indicated by colour of frame C) Outcome screen: Responses that do not meet the cutoff time result in a feedback of 'too late', correct answers are associated with a green smiley face (100 points for correct responses that meet a time requirement; 1 point awarded for correct responses that are too slow) and incorrect answers with a red smiley face.

Depression Severity

Hamilton Rating Scale for Depression – 17 item (HAMD-17)

The HAMD-17 is a widely used clinician administered scale to aid in the diagnoses of depression and will be used to confirm that patients meet at least moderate to severe symptoms (score of 17 or greater) (Hamilton, 1960).

3.5 Imaging Methods

3.5.1 Neuroimaging Acquisition

Neuroimaging consisted of both structural and functional MRI obtained at SMH utilizing a SIEMENS MAGNETOM Skyra 3T MRI scanner. A high-resolution image of each participant's brain was conducted through a whole-brain T1-weighted anatomical scan at 1.0 mm^3 resolution (8 minutes). The resting-state functional connectivity of each participant was captured using a whole-brain T2*-weighted BOLD 2D spin-echo Echo Planar Imaging (EPI) - series at a resolution of 4.0 mm^3 and a temporal resolution of 2000 ms during the awake resting state (10 minutes). These images were collected over a 200 mm field of view with an Echo Time (TE) of 30 ms and 75° flip angle.

3.5.2 Preprocessing

All neuroimaging analyses were conducted utilizing tools in the FMRIB Software Library (FSL) neuroimaging analysis program (Jenkinson et al., 2012). Prior to any preprocessing of rsfMRI data, each subjects' T1-weighted anatomical scan was processed through the Brain Extraction Tool (BET) to remove non-brain tissue (Smith, 2002). Repeated iterations of the main functions of BET were ran to allow for more robust brain centre estimation. Each file was assessed individually to ensure there was proper selection of brain matter.

FSL FMRI Expert Analysis Tool (FEAT) was utilized for the preprocessing of each subjects' 4D rsfMRI data (Woolrich, Ripley, Brady, & Smith, 2001). A default brain/background threshold of 10%, noise level of 0.66, temporal smoothness of 0.34 and Z-threshold of 5.3 were utilized.

To allow for T2* signal equilibrium stabilization, 5 volumes were deleted resulting in a final number of 295 volumes for each subject. Motion correction was conducted through Motion Correction using FMRIB's Linear Image Registration Tool (MCFLIRT), interleaved slice-timing correction, spatial smoothing (6mm) and global 4D-intensity normalization were applied (Jenkinson, Bannister, Brady, & Smith, 2002). High-pass temporal filtering was not yet conducted as it may reduce temporal degrees of freedom and impact later use of Independent Component Analysis – Automatic Removal of Motion Artifacts (ICA-AROMA) (Pruim et al., 2015). Linear registration to each subjects' main structural image was applied using Boundary-Based Registration (BBR), which utilizes both the original T1-weighted anatomical image and BET-extracted image via FSL FMRIB's Linear Image Registration Tool (FLIRT) (Greve & Fischl, 2009; Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001). Non-linear transformation of the T1-weighted and rsfMRI data to a standardized space was conducted via FSL FMRIB's Non-Linear Image Registration Tool (FNIRT) utilizing the MNI152 2 mm brain extracted image with a 4 mm warp resolution (Andersson, Jenkinson, & Smith, 2010; Fonov et al., 2009, 2011).

ICA-AROMA, which utilizes FSL Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC), was ran to identify and remove motion-related artifacts on each subjects' preprocessed rsfMRI data. The ICA-AROMA script was ran through Python 2.7 with the following inputs (Pruim et al., 2015): 1) The preprocessed rsfMRI data, 2) The mat-file describing the linear transformation of the subjects' rsfMRI data to their T1-weighted structural space obtained via FSL FLIRT, 3) The warp-file describing the non-linear transformation of the structural data to standard MNI152 space obtained via FSL FNIRT, 4) The 6 motion parameters obtained during volume-realignment obtained via MCFLIRT.

The default non-aggressive denoising option was selected which includes partial regression of each component. After completion of ICA-AROMA, each subjects' denoised rsfMRI data was inspected visually to ensure that the quality of the data remained. The data then underwent additional preprocessing, including high-pass temporal filtering (0.01hz).

3.5.3 Group Independent Component Analysis and Component Selection

The preprocessed data underwent Group Independent Components Analysis (gICA) through use of FSL MELODIC with multitemporal concatenation (Beckmann & Smith, 2004). Extraction was limited to 7 components to minimize underfitting of the data. Furthermore, the number of components were selected in accordance to a study by Yeo and colleagues which served as a reference for other functional connectivity studies. Yeo and colleagues utilized clustering algorithms which parcellate the cerebral cortex into 7 networks (Yeo et al., 2011).

After completion of the gICA, each component was assessed visually to select those with activation patterns resembling resting state networks of interest utilizing FSLeyes. The temporal power spectrum of the selected components was assessed to ensure they were appropriate for further analysis. Reference data of the salience network and the canonical reward networks from Yeo and colleagues were utilized in conjunction with these components to confirm the selection of the correct networks (Yeo et al., 2011). This was conducted by importing the NifTI files containing the components and reference networks into MATLAB as 3D matrices and running a dice coefficient analysis.

3.6 Statistical Analyses

All statistical analyses were carried out using SPSS version 23 for clinical and behavioural data, and FSL for neuroimaging analyses (IBM Corp., 2015). Sample size calculations for the primary analyses were conducted *a priori* by utilizing a target power of 0.80 and a type I error rate of 0.05 to determine an expected sample size. Given that studies which have analyzed the correlation between anhedonia and function in MDD are scarce, especially in the context of occupational function, correlation coefficients obtained in a study by Rungpetchwong and colleagues were determined to be most relevant for the primary analyses of this study (Rungpetchwong et al., 2017). Specifically, Rungpetchwong and colleagues identified the correlation between anhedonia severity and impairment in global function in participants with MDD (Rungpetchwong et al., 2017). Through utilization of their identified correlation coefficient

of 0.40 between anhedonia and global function, it was determined that a sample size of approximately 44 would be needed to detect a significant correlation between anhedonia and occupational function (Rungpetchwong et al., 2017). To provide additional insight, *post*-hoc power analyses with a specified power of 0.80 and type I error rate of 0.05 using our actual sample sizes and identified correlation coefficients between the LEAPS and DARS were conducted.

Participants with missing LEAPS scores due to retirement, unemployment, or long-term disability, were excluded from the analyses. All continuous variables were tested for normality and homogeneity by using Shapiro-Wilk tests and Levene's Test of Equality of Variances respectively prior to all subsequent analyses. Continuous variables determined to be parametric were further analyzed via independent samples t-tests to compare group differences. For non-parametric variables, the distributional shape between groups was further assessed to determine which test would be conducted. Mann Whitney U test were utilized to assess for group differences for non-parametric variables with an equal distributional shape. Non-parametric variables with unequal distributional shape between groups were assessed with independent samples t-tests with bootstrapping (2000 samples) and bias corrected accelerations to account for these differences. Differences in categorical variables were assessed using chi-square analyses. All analyses utilized a p value of < 0.5 to identify statistical significance unless stated otherwise

Demographic variables included age, sex, years of education completed, marital status, and employment status to ensure that the two groups were appropriately matched. Demographic variables with significant differences between groups would be utilized as covariates in subsequent analyses.

3.6.1 Objective 1: Relationship between Occupational Function and Anhedonia Scales

3.6.1.1 Primary Analysis – Relationship between the LEAPS and DARS

The relationship between the LEAPS (total score, percentage of work hours missed, and

productivity) and DARS scores (total score and all subscale scores) was assessed via bivariate correlational analyses within each group using either Pearson's product-moment correlations or Spearman's rank correlation coefficients according to normality. Correlation values with a magnitude between 0 to 0.30, 0.30 to 0.70 and 0.70 to 1.0 were considered weak, moderate and strong associations respectively (Akolgu, 2018). A Bonferroni correction was applied to the original *p*-value of 0.05 to account for multiple comparisons.

3.6.1.2 Secondary Analyses

Bivariate correlational analyses

The relationship between the LEAPS total score and subscale scores with the SHAPS were assessed within each group using the same analyses described in section 3.6.1.1. Correlation values with a magnitude between 0 to 0.30, 0.30 to 0.70 and 0.70 to 1.0 were considered weak, moderate, and strong associations respectively (Akolgu H, 2018).

Mean differences between MDD and Healthy Controls

Mean differences between MDD participants and healthy controls for the level of: 1) impairment in occupational function, measured by the LEAPS and 2) anhedonia, measured by the DARS and SHAPS, were analyzed with the appropriate statistical method as described above. These analyses included the Independent Samples t-tests (with or without bootstrapping), and Mann-Whitney U tests. Cohen's *d* was calculated to obtain the effect sizes, with values of 0.20, 0.50, and 0.80 indicative of small, medium and large sizes respectively (Cohen, 1988, 1992).

3.6.2 Objective 2: Relationship between Occupational Function and Reward-Tasks

3.6.2.1 Effort-Expenditure for Reward Task

The willingness to expend effort for reward and the effects of the variables of interest on this outcome was tested via generalized estimating equations and correlation analyses. Willingness to expend effort was defined as the proportion between selecting High Cost/High

Reward (HC/HR) options relative to selecting the Low Cost/Low Reward (LC/LR) options, for the overall task and for each probability level.

Generalized Estimating Equations

A general estimating equation (GEE) model was utilized to test for the main effects and relationship of the LEAPS and the probability of selecting the HC/HR option. Use of the GEE in EEfRT has the advantage of modeling the effects of time-variant and time-invariant factors on related measurement outcomes, such as multiple trials by one subject and can analyze variables with non-Gaussian distributions (Treadway 2009 Treadway 2012). The dependent variable was the dichotomous selection of HC/HR ('hard task') or LC/LR ('easy task') and the probability of selecting the HC/HR option was modeled using a binary logistic distribution. An unstructured working correlation matrix was selected for this dataset. Reward magnitude and reward probability were both coded as 'low', 'medium' and 'high' as defined previously. The model included reward magnitude, reward probability and expected value (the interaction effect between magnitude and probability) as factors and trial number as a covariate to account for task-related fatigue.

Bivariate Correlational Analysis

Bivariate correlational analyses were conducted between the proportion of HC/HR to LC/LR selections and scores on the LEAPS across each probability level and the entire task using either a Pearson's correlation coefficient or Spearman's rank coefficient according to normality.

3.6.2.2 Cued-Reinforcement Reaction Time Task

Differences in mean reaction times between participants with MDD and healthy controls across each reward probability was assessed via two-tailed independent t-tests. Incentive motivation was assessed by comparing differences in CRRT-RRS between groups across each reward contingency. CRRT-RRS values for each subject was acquired by subtracting the mean reaction time for low probability trials (10%) from the mean reaction time for high probability trials (90%). Incorrect trials and trials that exceeded the time limit of 2000 ms were excluded

from the mean reaction time analyses (Cools, 2005). The cut-off reaction time was calculated by subtracting the standard deviation and mean reaction time values from the second practice block for each reward contingency. The association between CRRT-RRS and the LEAPS (total score and subscale scores) (subscale and total score) were conducted via Pearson's correlations. The proportion of participants demonstrating reinforcement-related speeding were compared utilizing Chi-square tests between groups. A Repeated ANOVA was utilized to assess for differences in reaction time between blocks across each reward probability level between participants with MDD and healthy controls, with LEAPS total score as a covariate. Population variances were assessed by utilizing Mauchly's Test of Sphericity. Greenhouse-Geisser corrections were applied for data which violated assumptions of sphericity to obtain a more conservative result.

3.6.3 Objective 3: Neuroimaging Analyses and Occupational Function

Dual regression analyses were conducted to investigate group differences and associations with the LEAPS and DARS within each of the selected components (Beckmann, Mackay, Filippini, & Smith, 2009). LEAPS scores were utilized as both a continuous variable, and as a categorical variable using a median split. A general linear model with six exploratory variables (EVs) for: 1) MDD status 2) HC status 3) demeaned LEAPS score 4) Low LEAPS Score 5) High LEAPS score and 6) demeaned DARS score was created via FSL. For both the DMN and SN, contrasts were selected to create an appropriate design matrix for four analyses: 1) a two-tailed independent t-test between the MDD group and healthy control group, 2) correlation analyses between the components and demeaned total LEAPS scores utilizing the entire sample, 3) a two-tailed independent t-test between participants with low and high LEAPS scores, and 4) correlation analyses between the components and demeaned total DARS scores. . Standard settings were utilized, including variance normalisation, and 5000 permutations for randomise. A p value of < 0.05 was utilized to denote significance.

Chapter 4
Results

4.1 Demographics and Depression Severity

A total of 56 potential participants completed a screening visit to assess for eligibility, with 36 screened for the MDD group and 20 screened for the healthy control group (**Figure 4)**. A total of 43 participants were enrolled into the study, with 23 in the MDD group (*n* = 6 male, *n* = 17 female; mean age = 41.52 ± 13.24) and 20 in the healthy control group (*n* = 11 male, *n* = 9 female; mean = age 40.10 ± 15.10). In the MDD group, 3 participants were excluded from further analyses due to missing LEAPS scores, resulting in a sample of 20.

There were no statistically significant differences in demographic outcomes between MDD patients and healthy controls with respect to age, sex, years of education, employment, or student status and marital or domestic partnership status **(Table 2)**. Participants with MDD had a statistically higher mean HAMD-17 score of 21.83 ± 5.63 than healthy controls 0.95 ± 1.31 with a large effect size, $t(41) = -15.7$, $p < 0.001$, Cohen's $d = 4.95$.

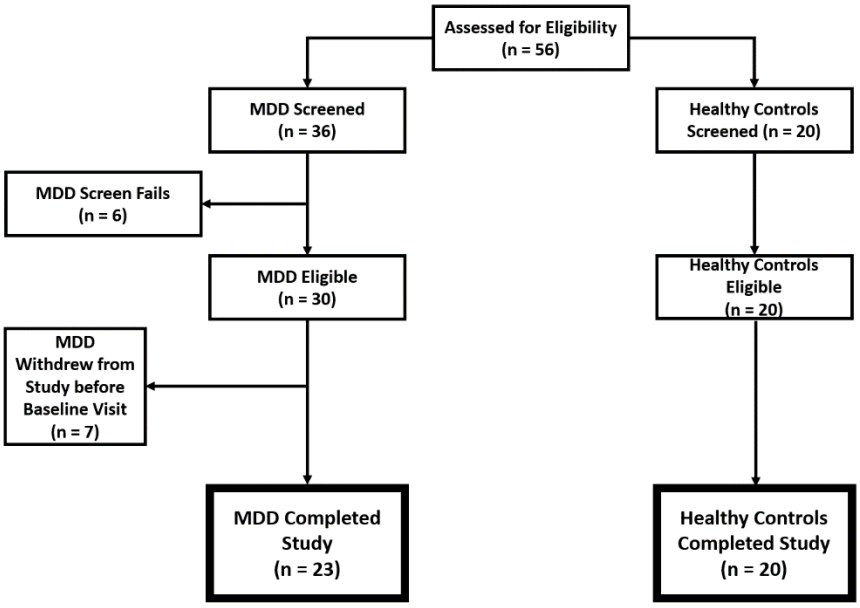


Figure 4. Enrolment of Participants with MDD and Healthy Controls.

Table 2. Demographic information and HAMD-17 scores of Participants with MDD (*n* = 20) and Healthy Controls (*n* = 20)

	MDD Group (n = 20) (Mean ± SD) or *n*	**Healthy Controls (n = 20) (Mean ± SD) or *n***	**Overall (n = 40) (Mean ± SD) or *n***	***p***	**Cohen's *d***
Age (years)	41.52 ± 13.24	40.10 ± 15.10	40.86 ± 13.98	0.744	0.10
Sex					
Male	6	11	17	0.053 [c]	-
Female	17	9	26		
Year of Education	15.04 ± 1.46	16.16 ± 2.46	15.55 ± 2.03	0.094 [b]	- 0.56
Employment Status					
Employed/Student	16	17	33	0.118[c]	-
Unemployed	7	2	9		
Marital Status					
Married/common-law	10	3	13	0.053 [c]	-
Not married	13	16	29		
HAMD-17	21.83 ± 5.63	0.95 ± 1.31	12.07 ± 11.17	<0.001 [a]	4.95

[a] Independent Samples T-test, 2000 bootstrap samples; [b] Mann-Whitney U Test; Chi-Square Tests; [c] Chi-Square Test

4.2 Objective 1: Occupational Function and Self-Report Anhedonia Measures

4.2.1 Primary Analysis – Relationship between the LEAPS and the DARS

After adjusting for multiple comparisons, a p-value of 0.001 was selected as cut-off for significance. There was a strong negative correlation between total LEAPS score and the total DARS score ($r_p(41) = -0.776$, $p < 0.001$) and all DARS subscales, with correlation coefficients ranging from -0.755 to -0.762, all $p < 0.001$ in the MDD group (**Table 3**). The percentage of work hours missed, and the LEAPS productivity subscale were not significantly correlated with the DARS total score or subscales. However, for the productivity subscale, there was a trending association with the DARS hobbies subscale *(p* = 0.006) and DARS total score (*p* = 0.024). No significant correlations were identified between the LEAPS and all anhedonia scores for healthy controls.

Since our total sample size was 40, our study may be underpowered relative to the expected sample size of 44 during the *a priori* sample size calculation. After conducting a *post-hoc* power analysis utilizing our correlation between LEAPS total score and the DARS total score, we identified that there was a power of 0.998 for our MDD group. For the correlations between the DARS total score and work hours missed and productivity levels, respectively, our study had a power of 0.536 and 0.842. These power analyses suggest that our study was adequately powered for LEAPS score and productivity levels, but not work hours missed.

4.2.2 Objective 1: Secondary Analyses

4.2.2.1 Relationship between the LEAPS and the SHAPS

After adjusting for multiple comparisons, there was a strong positive correlation between the total LEAPS score and the SHAPS score in the MDD group ($r_s(41) = 0.719$, $p < 0.001$; **Table 2**). No significant correlations were identified between either LEAPS subscale and the SHAPS in the MDD group. For healthy controls, the LEAPS total score and the LEAPS subscale scores were not significantly correlated with the SHAPS.

Table 3. Bivariate correlation analyses between Self-Report Anhedonia measures and Occupational Function within Groups

	DARS										SHAPS	
	Hobbies		Food/Drink		Social		Sensory		Total			
	MDD	HC	MDD	HC	MDD	HC	MDD	HC	MDD	HC	MDD	HC
LEAPS												
% Work Missed	-0.409[b]	0.292[b]	-0.337[b]	0.238[b]	-0.303[b]	0.410[b]	-0.444[b]	0.094[b]	-0.409[b]	0.238[b]	0.572[b]	0.293[b]
Productivity	-0.639[b]	0.377[b]	-0.436[b]	0.095[b]	-0.357[b]	0.198[b]	-0.430[b]	0.135[b]	-0.544[b]	0.252[b]	0.307[b]	0.251[b]
Total	**-0.755**[**b]	0.014[b]	-0.647[a]	-0.059[b]	**-0.760**[**a]	-0.229[b]	**-0.762**[**a]	0.237[b]	**-0.776**[**a]	-0.043[b]	**0.719**[**a]	0.150[b]

Significant correlations after Bonferroni correction bolded for clarity; ** significant correlation $p < 0.001$ after Bonferroni correction; [a] Pearson Product Moment Correlation; [b] Spearman's rank-order correlation; MDD = Participants with Major Depressive Disorder ($n = 20$); HC = Healthy Controls ($n = 20$)

4.2.2.2 Mean Differences between the MDD Group and Healthy Controls

Overall degree of impairment in occupational function, indicated by the total score on the LEAPS, was significantly greater in participants with MDD than healthy controls with a large effect size (*M* = 15.17, *SD* = 6.08; *M* = 2.00, *SD* = 2.45, respectively), $t(41) = -8.7$, $p < 0.001$, Cohen's $d = 2.77$. The MDD group had significantly higher levels of percentage of work hours missed than healthy controls (*M* = 40.13%, *SD* = 44.16%; *M* = 3.32%, *SD* = 9.95% respectively), indicative of higher levels of absenteeism, $U = 85$, $p = 0.004$. Productivity levels, measured by the LEAPS productivity subscale, were significantly lower in participants with MDD relative to healthy controls, with a large effect size (*M* = 4.16, *SD* = 3.04; *M* = 1, *SD* = 3.00 respectively), $t(41) = -3.1$, $p = 0.004$, Cohen's $d = 2.77$ (**Table 4**).

Participants with MDD had significantly lower total DARS score than healthy controls (*M* = 35.06, *SD* = 19.00; *M* = 9.00, *SD* = 4.73 respectively), indicative of higher levels of anhedonia in MDD. Significant differences across all DARS subscales between participants with MDD and healthy controls were found, with participants with MDD having higher levels of anhedonia in each domain (**Table 4**). Anhedonia measured by the SHAPS was significantly higher in participants with MDD compared to healthy controls (*M* = 5.61, *SD* = 4.02*; M* = 0.47, *SD* = 0.96 respectively), $t = -5.4$, $p < 0.001$.

Table 4. Differences in Function and Anhedonia between the MDD Group and Healthy Controls

Variable	MDD Group (n = 20) (Mean ± SD)	Healthy Controls (n = 20) (Mean ± SD)	Overall (n = 40) (Mean ± SD)	*p*	Cohen's *d*
LEAPS					
Work Hours Missed (%)	40.13 ± 44.16	3.32 ± 9.95	23.66 ± 37.96	0.004[a]	1.11
Productivity	4.16 ± 3.04	1 ± 3.00	2.71 ± 3.37	<0.001[b]	1.05
Total	15.17 ± 6.08	2.00 ± 2.45	8.41 ± 8.06	<0.001 [a]	2.77
DARS					
Hobbies	9.00 ± 4.73	15.05 ± 1.75	11.86 ± 4.70	<0.001 [a]	- 1.65
Food/Drink	8.94 ± 4.45	14.05 ± 2.46	11.38 ± 4.25	0.001 [a]	- 1.39
Social	6.83 ± 4.68	14.53 ± 2.04	10.76 ± 5.24	<0.001 [a]	- 0.95
Sensory	10.28 ± 6.29	18.58 ± 2.19	14.05 ± 6.11	<0.001 [a]	- 1.71
Total	35.06 ± 19.00	62.21 ± 7.47	48.05 ± 19.26	<0.001 [a]	- 1.83
SHAPS	5.61 ± 4.02	0.47 ± 0.96	3.28 ± 3.85	<0.001 [a]	- 0.76

[a]Independent Samples T-test, 2000 bootstrap samples; [b] Mann-Whitney U Test; significance considered at $p < 0.05$.

4.3 Objective 2: Occupational Function and Reward-Task Performance

4.3.1 Effort-Expenditure for Reward Task

A GEE model was utilized to test for the main effects of the LEAPS on the selection of hard task options, which is indicative of a greater willingness to expend effort for reward, as seen in **Table 5**. This model included reward magnitude, reward probability and expected value as factors and trial number as a covariate to account for task-related fatigue. Increases in impairment in occupational function (total LEAPS) was a significant predictor of decreases in selection of hard task options (b = - 0.037, p = 0.004). Higher reward magnitude, reward probability and expected value were associated with an increase in the proportion of hard tasks selected.

Table 5. EEfRT Generalized Estimating Equation Model

Variables	*b* coefficient	SE	P
Reward Magnitude	0.245	0.0386	<0.001*
Reward Probability	0.454	0.0387	<0.001*
Expected Value	0.117	0.0326	<0.001*
Trial Number	0.005	0.0016	0.001*
LEAPS	- 0.037	0.0121	0.004*

* significant correlation p < 0.05.

Bivariate analyses were conducted between the LEAPS and the proportion of hard task selection across each probability level of the EEfRT task as seen in **Table 6**. LEAPS productivity, percentage of work missed and total score, were not significantly related to hard task selection (**Table 6**).

Table 6. Correlations between proportion of Hard-Task choices at each probability level and Impairment in Occupational Function

Variable	Proportion of Hard-Task Choices			
	12%	50%	88%	All Trials
LEAPS				
Work Hours Missed (%)	0.038ǂ	0.222ǂ	0.195ǂ	0.229ǂ
Productivity	0.200ǂ	0.306ǂ	0.308ǂ	0.324ǂ
Total	0.138ǂ	0.105ǂ	0.059ǂ	0.092ǂ

* significant at $p < 0.05$; ǂ Spearman's correlation

4.3.2 Cued-Reinforcement Reaction Time Task

The Chi-square test resulted in no significant differences in reinforcement-related speeding (positive values indicative of no reinforcement-related speeding and negative values indicative of reinforcement-related speeding) between the MDD group and healthy controls ($\chi^2(1) = 2.16$, $p = 0.142$). This indicates that there were no differences in the level of incentive motivation or degree of wanting between the study groups.

The mean reaction time and standard deviations for reaction times across each probability and block can be found in **Table 7**. Mauchly's Test of Sphericity was violated for reward probability and the interaction between probability and block (both p <0.001), thus Greenhouse-Geisser corrections were utilized (probability Ɛ = 0.712; probability and block Ɛ = 0.678). The difference between means is not significantly different between probability, block, their interaction and interactions with the LEAPS and group as seen in **Table 8** (all $p > 0.05$).

Table 7. Mean reaction times differences on CRRT trials at each reward probability level

Variable	MDD Group (Mean ± SD)	Healthy Controls (Mean ± SD)	Overall (Mean ± SD)	*t (df)*	*p*
Block 1					
Low Probability	744.11 ± 173.39	656.88 ± 123.27	699.32 ± 154.10	-2.113	0.041
Medium Probability	763.28 ± 194.83	674.25 ± 136.92	717.56 ± 171.27	-1.897	0.065
High Probability	765.49 ± 173.64	668.80 ± 134.38	717.84 ± 173.64	-2.086	0.044
Block 2					
Low Probability	733.89 ± 172.64	637.29 ± 128.40	684.28 ± 157.20	-2.055	0.046
Medium Probability	724.56 ± 161.52	625.97 ± 111.73	673.93 ± 145.11	-2.369	0.023
High Probability	724.47 ± 181.84	615.33 ± 111.06	668.43 ± 157.61	-2.453 (37.96) ǂ	0.019
Both Blocks					
Low Probability	751.64 ± 168.33	654.76 ± 124.58	706.58 ± 155.73	-2.117	0.040
Medium Probability	758.31 ± 177.39	657.28 ± 123.07	711.32 ± 161.04	-2.137	0.039
High Probability	758.18 ± 184.92	649.91 ± 122.47	707.82 ± 166.38	-2.289 (38.46) ǂ	0.028

ǂ signifies equal variances not assumed. *df* = 41 unless otherwise noted. Independent Samples T-test. Low probability = 10%; Medium Probability = 50%; High probability = 90%;

Table 8. CRRT Repeated Measures ANOVA

Variables	*F*	df	*p*
Probability	3.145	1.424, 48.413	0.068
Probability*LEAPS	0.199	1.424	0.744
Probability*Group	0.789	1.424	0.421
Block	0.297	1, 34	0.589
Block*LEAPS	0.035	1	0.852
Block*Group	0.193	1	0.663
Probability*Block	0.601	1.357, 46.128	0.490
Probability*Block*LEAPS	0.694	1.357	0.451
Probability*Block*Group	0.381	1.357	0.604

4.4 Objective 3: Neuroimaging Results

Components from gICA

Through visual inspection, only one of the seven extracted components were determined as noise. Of the six remaining components, two were determined as the DMN and the other as the SN by utilizing reference networks from (Yeo et al., 2011) and the Dice coefficient. Component 4 was identified as the DMN (X +6, Y -11, Z +25; Z = 3.5) and component 5 was identified as the SN (X +1, Y +4, Z +31, Z = 4.5) as seen in **Figure 5**.

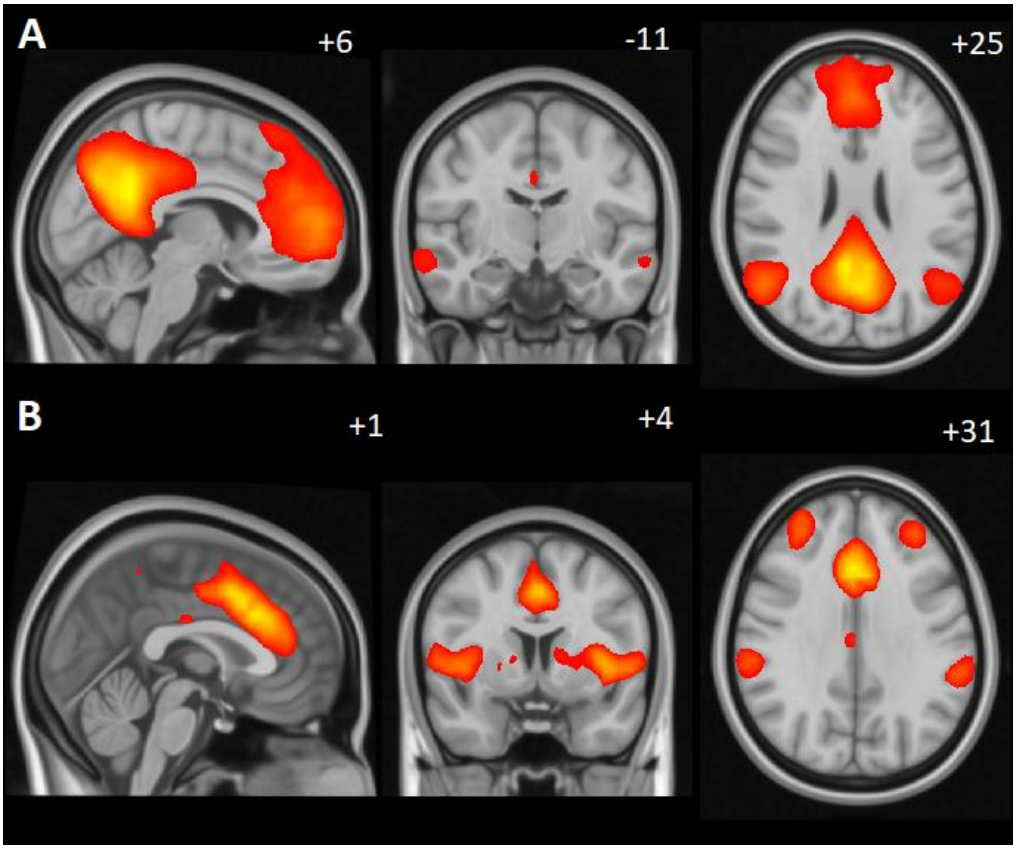


Figure 5. Functional connectivity results from gICA visualized onto MNI152 0.5 mm standard space **A)** Component representing the default-mode network (red-yellow, 3.5 < z-score < 14.6) and **B)** Component representing the salience network (red-yellow, 4.5 < z-score < 9.1).

Dual Regression Analyses

No significant differences in resting-state functional connectivity were identified

between participants with MDD and healthy controls in either the DMN or the SN. Furthermore, there were no significant correlations with total LEAPS score with either the DMN or SN across the entire sample, nor was there a significant difference between the group with low LEAPS score and high LEAPS scores (**Figure 6**). No significant correlations with the total LEAPS score or total DARS score with either the DMN or the SN was identified. Similar results were found after adjusting the *p*-value to 0.1. Post-hoc analyses using the lowest effect size of 0.196, found in the anterior cingulate cortex revealed that a sample size of 199 would be required to identify significance at p = 0.05 and a power of 0.80.

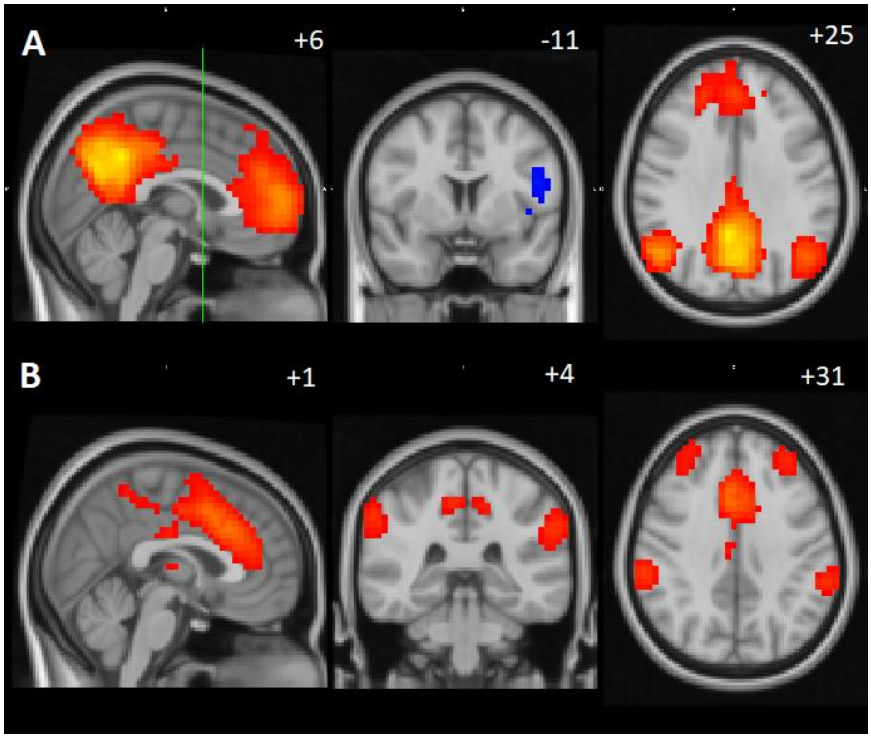


Figure 6. Results of dual regression analyses. A) Differences in activity in the DMN B) Differences in activity in the SN. No significant differences in functional connectivity were identified between the study groups, LEAPS groups. There was also no significant correlation identified with the total LEAPS score or total DARS score. Therefore, only the network of interest was highlighted in all dual regression analyses, resulting in the same image for each analysis. Red-yellow scale represents the activity of the network of interest, and blue-light blue represents decreases in activity. Areas with significant differences in activity would have been represented in green.

Chapter 5

Discussion

5.1 Executive Findings

In the present study, it was demonstrated that functional impairment in the occupational domain was strongly associated with anhedonia severity in participants with MDD but not healthy controls. More specifically, our primary results demonstrated that overall level of impairment in occupational function, measured by total LEAPS scores, was strongly correlated with the total DARS score, and all DARS subscales, except for food/drink in the MDD group. Specific aspects of occupational function, such as the percentage of hours missed at work or productivity levels were not associated with anhedonia. The MDD group demonstrated significantly higher levels of both functional impairment in the occupational domain and anhedonia severity compared to healthy controls. The behavioural reward task results suggest that the willingness to expend effort may be associated with occupational function, but incentive motivation may not be. Finally, while the independent components analyses suggests that functional connectivity in the DMN and SN may not be significantly correlated with the LEAPS nor the DARS, this may be a result of the analyses being inadequately powered; therefore these results should be interpreted tentatively. No significant differences in DMN or SN activity at rest were identified between the MDD group and healthy controls. These findings demonstrate a more comprehensive understanding of the link between impairment in occupational function and anhedonia in MDD through clinical self-report scales, behavioural reward-tasks and neuroimaging. By providing direct insight into the relationship between function and anhedonia, these findings suggest anhedonia may be a potential treatment target to alleviate functional impairment in MDD.

5.2 Objective 1: Occupational Function and Self-Report Anhedonia Measures

The present study implemented a more rigorous evaluation of the relationship between impairment in occupational function and anhedonia in MDD than prior studies. Previous studies have utilized more broad measures of functional impairment, such as the SDS, which may not capture important factors related to occupational function, such as motivation and effort (Cao et al., 2019; Lam et al., 2014, 2017; Rungpetchwong et al., 2017). The primary objective of this study was to elucidate the association between impairment in occupational function in MDD, measured by the LEAPS, and anhedonia severity, measured by the DARS. Overall occupational impairment was strongly correlated with overall anhedonia in the MDD group but not healthy controls. Our results were in line with our primary hypothesis and consistent with the limited findings in the current literature (Cao et al., 2019). Furthermore, overall occupational impairment was strongly correlated with all DARS subscales except for the food/drink domain. While we hypothesized that all DARS subscales would be associated with overall occupational impairment due to the assessment of motivation and effort in each anhedonia domain, this was not the case. However, our results may suggest that there may be certain domains of anhedonia (e.g. social activities) which are more closely related to occupational function. For example, given that work commonly involves social aspects, it is not unreasonable to expect that impairment in occupational function is more strongly associated with social anhedonia rather to appetitive anhedonia (Lam et al., 2017). Also as hypothesized, our results revealed that total occupational impairment was significantly associated with SHAPS score, which lends more support for the strong association between anhedonia and occupational impairment. Furthermore, the associations between overall occupational impairment and anhedonia, measured by both the DARS and SHAPS, remained significant after a conservative Bonferroni correction, which attests to the robustness of this relationship.

In contrast to overall occupational impairment, reduced work productivity levels and increased percentage of hours missed from work were not significantly associated with

anhedonia on either the DARS or SHAPS in both the MDD group and healthy controls. These finding were inconsistent with our hypothesis, as we predicted that the LEAPS productivity score and hours missed would be associated with anhedonia. Given that our initial power analyses revealed that a sample size of 44 would be required to identify a significant correlation between occupational function and anhedonia, our findings may have been due to the study being underpowered. Furthermore, *post-hoc* power analyses revealed that for our results, our sample size for productivity levels was adequate, but not for percentage of work hours missed. Notably, the correlation between the DARS and productivity levels was significant but did not survive correction for multiple comparisons. Bonferroni corrections are considered more conservative, therefore a future study involving fewer comparisons would be likely to find significance (Perneger, 1998). Finally, the MDD group demonstrated greater impairment in overall occupational function, higher percentage of hours of work missed and reduced productivity levels compared to healthy controls, similar to findings by Lam and colleagues (Lam et al., 2014). In summary, our findings related to the primary study objective provide important insight into the relationship between occupational function and anhedonia, which suggests that the association may vary and that the underlying relationship is more complex than initially identified. Overall occupational impairment may be more strongly associated with various domains and facets of anhedonia, which has important implications for exploring anhedonia as a treatment target to aid in the alleviation of functional impairment in MDD.

5.3 Objective 2: Relationship between Occupational Function and Reward-Tasks

To supplement our primary objectives, computer-based behavioural tasks designed to probe incentive motivation and effort-expenditure were utilized to assess the specific impact of these reward facets on function. In the tested GEE model, the total LEAPS score was associated with the selection of choices requiring more effort after controlling for reward magnitude, reward probability, expected value and task-related fatigue, consistent with current literature (Park et al.,2017; Subramanipillai et al., 2019; Treadway et al., 2009). Greater occupational

function was associated with a lower selection of hard tasks, in line with our hypothesis. Given that low effort-expenditure has been associated with increased presenteeism at work, these findings were expected (Lam et al., 2012, 2017; Park et al., 2017). However, while the LEAPS was a significant contributor of the selection of hard task choices in the GEE model, it was not correlated with the mean proportion of hard task choices across each level of reward probability. While these findings are inconsistent with each other, it is important to note some limitations which may have impacted these results. The size of our study sample was inadequate to include additional covariates into our GEE models, despite their potential importance on effort-expenditure since we aimed to have approximately 10 subjects per variable tested. Given that we needed to include reward magnitude, reward probability, expected value and trial number in our models to allow our results to be compared to other studies utilizing the EEfRT task, we were unable to include other covariates such as group status or depression severity. Furthermore, we were unable to test the interaction effects of the LEAPS with reward magnitude and probability which may have altered the main effect of these scales independently. Indeed, further exploration utilizing a larger sample size is required to better elucidate the relationship between impairment in occupational function with behavioural presentations of reduced effort. Together, these findings may suggest that levels of effort may have an impact on function. Additional studies that isolate the effect of other variables, such as depressive symptom severity, are needed to better understand this relationship.

In examining incentive motivation using the CRRT, no significant interaction effects among reward probability, group, or the LEAPS were found when tested in various combinations. These results are inconsistent with our hypothesis which proposed that reduced incentive motivation would be associated with higher levels of occupational impairment given that the current literature has emphasized the importance of motivation to work (Lam et al., 2012). Incentive motivation was assessed by measuring CRRT-RRS, which is the mean difference in reaction time between low probability trials and high probability trials. Participants in the MDD group were expected to have CRRT-RRS values of a lower magnitude, which is indicative of lower levels of incentive motivation, than healthy controls. However, analysis via repeated

measures ANOVA revealed no significant differences in CRRT-RRS between groups and there was no significant relationship with reward probability or the LEAPS. It is important to note that these results also differ from other studies which have utilized the CRRT. Generally, reward probability, block and MDD status were significantly related to CRRT-RRS.

Independent t-tests revealed significant differences in mean reaction time between the MDD group and healthy controls on the CRRT task, with exception of the medium reward probability in Block 1. MDD participants were slower to respond when selecting the 'odd-one-out' across all probability levels and blocks, suggestive of lower motivation levels in this group. Ultimately, these findings suggest that there may be a relationship between functional impairment in MDD with level of effort-expenditure, but not incentive motivation; however, further exploration is needed.

5.4 Objective 3: Occupational Function and Resting-State Networks

Of the seven components extracted through ICA, two of the components were determined to be the DMN and SN after analyses with reference networks; however, the VMN was not extracted in these components. No significant differences in either network was identified between the MDD group and healthy controls. This is inconsistent with the literature given that other studies have been able to identify a difference in functional connectivity in these regions between participants with MDD and healthy controls (Fresco et al., 2017; Nishimura et al., 2015; Sambataro et al., 2014). Furthermore, there was no significant correlation between functional connectivity in these regions and overall functional impairment measured by the LEAPS. Similarly, no significant differences were identified when participants were categorized into low and high LEAPS scores. These findings were unexpected given what we currently know about the SN and DMN. The former is involved in executive control, task switching and integrating information associated with salient stimuli to modulate the activity of other networks for goal-driven behaviours (Gradin et al., 2011; Steffens, Wang, & Pearlson, 2019). Anhedonia, measured by the DARS, was also not significantly correlated with functional

connectivity in either the DMN or the SN. Given that other studies have identified the importance of these networks in goal-driven behaviours important to anhedonia (Kumar et al., 2017; Park et al., 2017), these findings were unexpected.

Given that proper execution of goal-driven behaviours is important to adequate function (Park et al., 2017), we had expected a correlation between occupational function and anhedonia and functional connectivity in these networks. The DMN is associated with self-reflection and the integration of memories and information for future goals and motivations (Alexopoulos et al., 2012; Sharma et al., 2017), Furthermore, the DMN also includes several important regions that have been implicated in reward processing, such as the vmPFC and PCC. Taken together, we had hypothesized that functional connectivity in this network would correlate with occupational function. However, despite their hypothesized role in occupational function, there are plausible explanations for our findings. The DMN is generally more active at rest than during goal-directed behaviour, thus the DMN may play a more diminished role in occupational function (Sambataro et al., 2014). Although altered connectivity in the DMN in MDD has been identified in other studies, it was largely associated with depressive symptoms, such as sleep disturbances, rumination and excessive worry, and remission rates (Sambataro et al., 2012). The DMN may have less utility in the assessment of impairment in occupational function as opposed to other domains, such as social function (Alexopoulos et al., 2012). For example, Kumar and colleagues identified greater activation in areas associated with the DMN in response to social exclusion (Kumar et al., 2017). However, there appears to be evidence which suggests that the activity of the DMN is composed of interactions among several subnetworks that may be impacted differently across patients with MDD (Sambataro et al., 2014). Therefore, it may be plausible that specific subnetworks are associated with occupational function which was not detected due to factors such as sample size.

Although the lack of significant correlation identified between the SN and occupational function was unexpected, findings from the current literature may provide a plausible explanation. The SN is primarily active during the evaluation of salient stimuli to modulate the activity of other networks to initiate goal-driven behaviours, which have been implicated to play a role in occupational function (Seely et al., 2007; Yeo et al., 2011). Other studies have

reported increased connectivity in the SN associated with increased response times to salient stimuli (Seely et al., 2007). Since these participants were assessed at rest, without any motivating stimuli or task, the differences in functional connectivity may have been less distinguishable between groups and a relationship with function or anhedonia more difficult to identify.

Lastly, given that occupational function often involves goal-driven behaviour, altered activity in networks such as the DMN may be less important than other networks, such as the VMN. Ideally, if we were able to extract a network that resembled the VMN from our ICA, this could have been tested. This is especially true given that other studies have demonstrated altered functional connectivity in the VMN related to impaired cost-benefit calculations required for effort-based decision making (Park et al., 2017). Future studies may look to utilize larger sample sizes to confirm whether the DMN, SN or VMN are involved with occupational function. Seed-based approaches may also be relevant to explore brain regions involved in reward-processing and occupational functioning, including the VMN.

5.5 Limitations

The present study has several limitations which should be noted. Although there were large effect sizes identified for the LEAPS total score, work hours missed and productivity score, the number of participants limited the number of variables that could be tested in each of the analyses. While significant associations were identified between occupational function and anhedonia via correlational analyses, the predictive value of the DARS on the LEAPS was not assessed due to sample size constraints. Use of regression analyses to include the main effects and interaction effects of each the DARS total score and subscale scores on occupational function would have provided important insight on the directionality of this association. Furthermore, the effects of other potential contributors of occupational impairment were not assessed due to sample size limitations. For example, depression severity and group status were not assessed alongside the DARS since the sample size was not adequate to address multicollinearity. Given that there was a strong correlation between the HAMD-17 score with

the DARS, SHAPS and LEAPS the predictive value of anhedonia may have not been entirely isolated from depression severity or MDD status. Since the primary purpose of this study was to identify whether occupational function was associated with self-report anhedonia, this limitation was accepted. Similarly, our sample size limited the number of variables which could be tested in the EEfRT GEE model, limiting our ability to test for the main effect of the DARS and its interaction with the LEAPS. The small sample size also influenced the power and number of resting state analyses that could be conducted. Additionally, since ICA is a data driven method, only two components were analyzed to compare group differences in activation and the association with the LEAPS and the DARS (Wu et al., 2018). Therefore, our sample sizes may have been underpowered to detect differences or correlations with our data. For example, some studies which have identified differences between participants with MDD and healthy controls have utilized approximately 200 subjects in each group, whereas others were adequately powered with 32 MDD participants and 36 healthy controls (Li et al., 2018; Zhi et al., 2018). Ideally, the interaction effects between the LEAPS and the DARS would have been included via principal components analysis. However, given that the primary objective was to assess the relationship between occupational function and anhedonia measured via self-reports, the limited and exploratory nature of these analyses was sufficient for the purposes of this study.

In addition to the impacts of sample size, it is also important to elaborate on limitations with respect to our methodology. Firstly, the inclusion and exclusion criteria for this study may not have adequately represented the desired sample. Since this study was embedded into a larger clinical trial of desvenlafaxine, participants in the MDD group were required to meet criteria with respect to current and past psychotropic medication use. Therefore, our sample may not be entirely representative of patients with MDD, such as those who are treatment resistant. Furthermore, participants who were retired, unemployed or on long-term disability were not excluded from enrolment into the study. Since the LEAPS measures occupational function of individuals specifically working in the past two weeks, 3 participants in the MDD group were unable to complete the assessment and were excluded from further analyses. Aside from reducing the power of our analyses, the exclusion of participants who are on long-term

disability, may inadvertently exclude those with severe impairment in occupational function. As a result, our results are limited to those who may be functioning well enough to continue working and may not be generalizable to all MDD patients.

With regards to the reward-tasks utilized in this study, there are limitations that should be acknowledged. While the EEfRT task was designed and validated to effort expenditure via monetary rewards, other underlying factors may have influenced the decision-making process of our participants. More specifically, the time to complete the easy trials of the task was 7 seconds compared to the 21 seconds required for the hard trials. As a result, this lower time to completion may have influenced participants to select the easy version of the task and have a confounding effect on our analyses.

While use of rsfMRI has merits in exploratory analyses, there are certain drawbacks, especially in the context of function. Restricting the parcellation of our resting-state date to 7 networks to match the Yeo networks also failed to isolate the VMN, which may have a role in function. Furthermore resting-state analyses may fail to capture changes in brain activity associated with goal-based decision making, which is implicated to have a role in occupational function (Park et al., 2017; Seely et al., 2007). This research question would be more adequately answered using task-based fMRI.

Chapter 6

Conclusions and Future Directions

In conclusion, the findings from this study demonstrated that impairment in overall occupational function is strongly associated with anhedonia severity in patients with MDD. Furthermore, by utilizing clinical, behavioural and neurobiological measures of anhedonia, we were able to acquire a more comprehensive understanding of the relationship between occupational impairment and anhedonia in MDD. As a core symptom of MDD, anhedonia has implications as a potential treatment target to alleviate impairment in occupational function through improvements in levels of motivation and effort. The behavioural tasks utilized in this study provided further insight into this relationship by demonstrating that levels of effort, rather than motivation, may have a greater impact on certain aspects of function. Finally, although the neuroimaging results did not identify a significant relationship between the DMN and SN with occupational function and anhedonia, it is possible that other resting-state networks, such as the VMN, are associated.

Further studies are required to refine our understanding of the link between anhedonia, reward processing and functional impairment. While the findings of this study suggest that the DARS is strongly associated with baseline levels of functional impairment, the mechanisms underlying the relationship between anhedonia and function require further elucidation. Although the findings of this study suggest that effort levels, but not motivation may play a role in this relationship, direct measurements of motivation, energy and effort should be used in conjunction with the DARS. Use of self-report scales and behavioural tasks which isolate and probe these facets of reward may provide important insight into the link between anhedonia and function. While motivation and effort have been implicated as important facets both in this study and the current literature, other aspects of reward processing such as interest and anticipation should also be studied in the context of function.

This study provided a preliminary comprehensive analysis of the link between occupational function and anhedonia in MDD by utilizing clinical self reports, behavioural reward-tasks and neuroimaging to better understand this complex relationship. Future studies

should aim to gain a more comprehensive understanding of this relationship that is more generalizable to a broader sample of patients with MDD. While the LEAPS assessed presenteeism and absenteeism, it was limited to those who were working. Therefore, additional measures of occupational function should be utilized to include those who may be experiencing severe occupational impairment, such as those who are on long-term disability. With respect to reward-tasks, other versions of the EEfRT task which remove the impact of time to completion may allow for a more accurate assessment of the relationship between effort and function. Furthermore, reward-tasks should be utilized in conjunction with task-based fMRI to develop a greater understanding of how the behavioural and neurobiological components of reward may interact and impair function in MDD. More specifically, effort and motivation-based tasks may be an adequate starting point given their impact on occupational function. In addition, since recovery of function is often a priority for patients with MDD, clinical trials which directly assesses the impact of various therapies should also be conducted to inform current treatment regimens. Lastly, given the wide range of functional impairment in MDD, other domains apart from occupation should be assessed, including more detailed analyses of social function and functional capacity. Given the evidence which suggests that functional capacity differs from functional performance, understanding its relationship to anhedonia is necessary to obtain a more complete understanding. Future studies should assess its relationship with the DARS using behavioural tasks which reflect modern tasks related to function. Ultimately, our findings from the self-report and behavioural tasks demonstrated that anhedonia may be strongly associated with functional impairment in the occupation domain and provided insight into this complex relationship.

Appendix 1

Screening Measures

Clinical Scales	Health and Medical history	Other
MINI	Medical History Exam	Informed Consent Form
HAMD-17	Physical Exam	Drug Screening (Blood & Urine)
MADRS	Depression History	Demographics Form
	ATHF	MRI Screening Form
	Pre-treatment Averse Events	

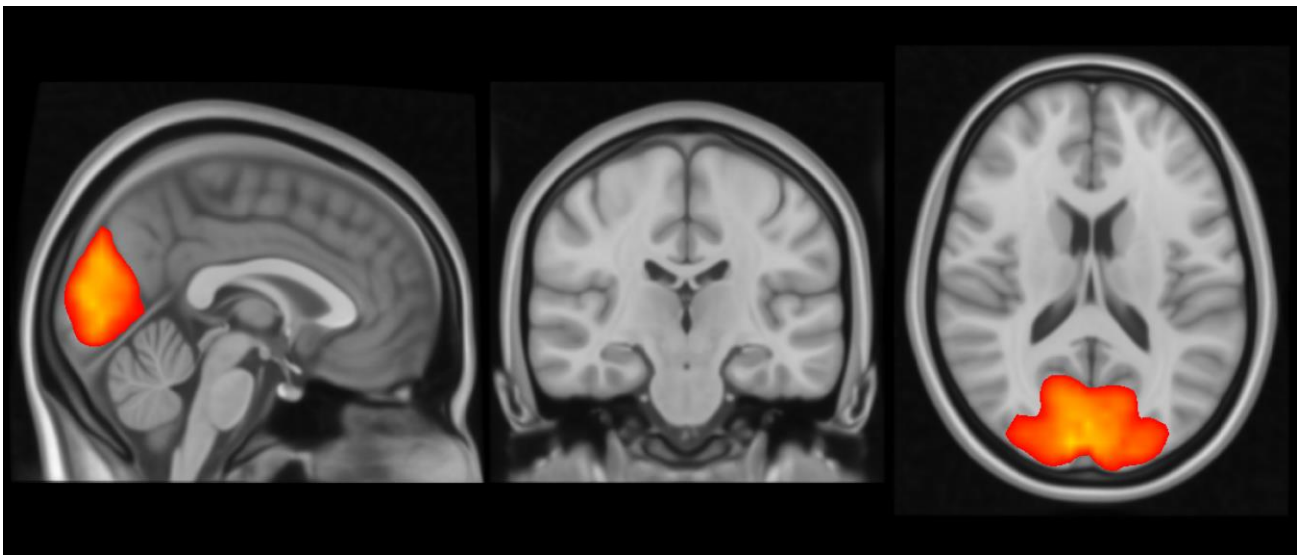
Appendix 2

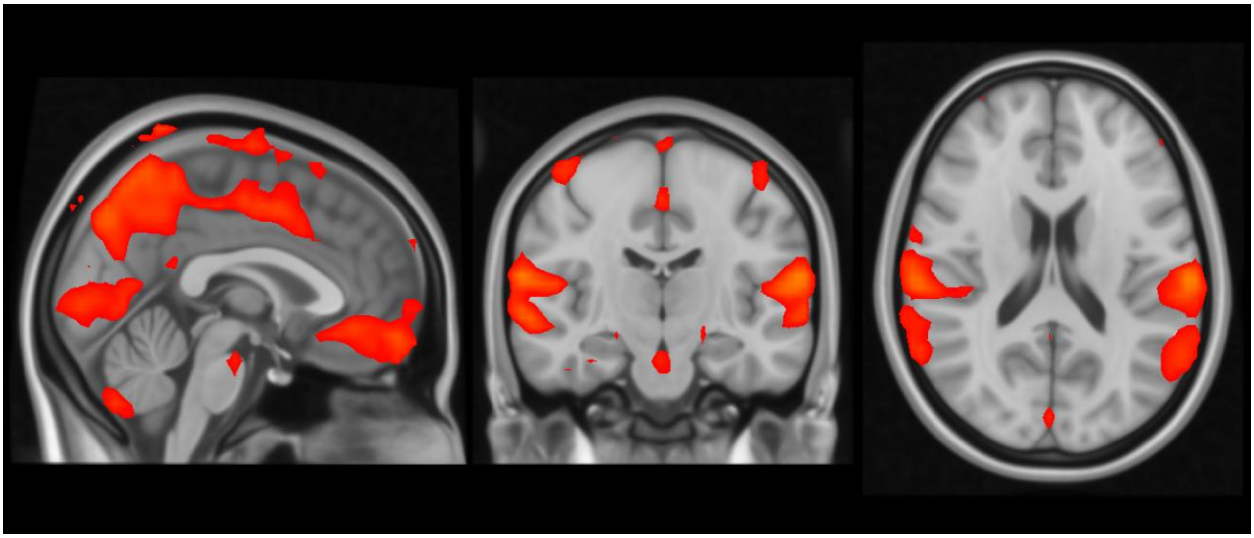
Shapiro-Wilk Tests

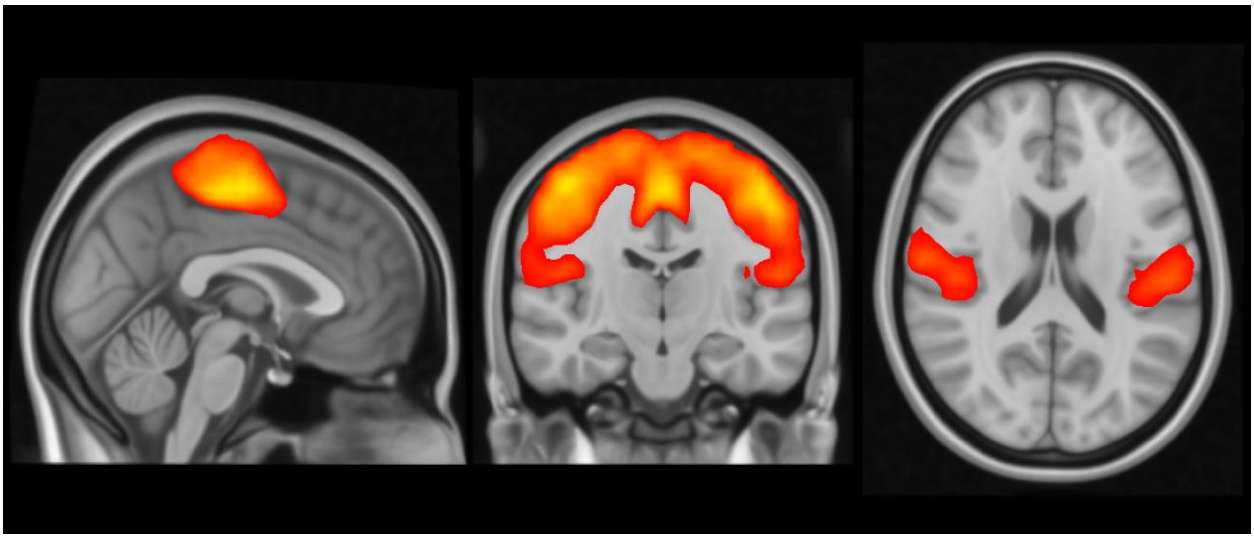
Variable	Shapiro-Wilk		p		Normality
	MDD	HC	MDD	HC	
Age	0.942	0.929	0.202	0.146	Yes
Years of Education	0.826	0.914	0.001	0.086	No
HAMD-17	0.884	0.739	0.120	<0.001	No
DARS					
Hobbies	0.892	0.638	0.021	<0.001	No
Food/Drink	0.926	0.819	0.102	0.002	No
Social	0.940	0.764	0.197	<0.001	No
Sensory	0.931	0.747	0.127	<0.001	No
Total	0.953	0.810	0.357	0.001	No
SHAPS	0.966	0.537	0.595	<0.001	No
LEAPS					
Work Hours Missed (%)	0.741	0.409	<0.001	<0.001	No
Productivity	0.925	0.384	<0.001	0.139	No
Total	0.964	0.898	0.689	0.001	No

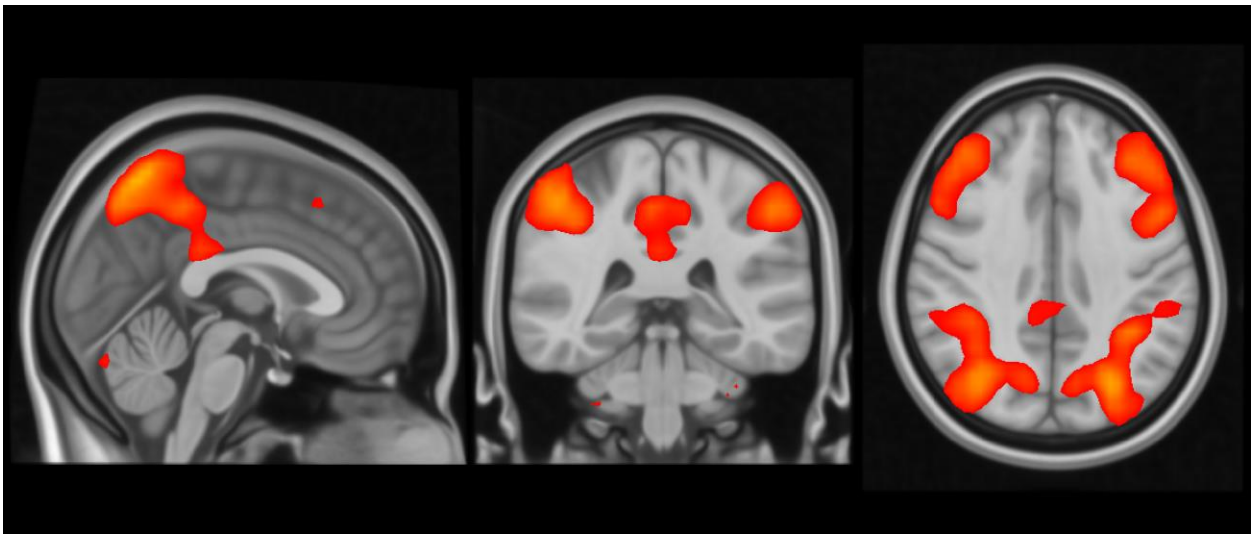
Appendix 3

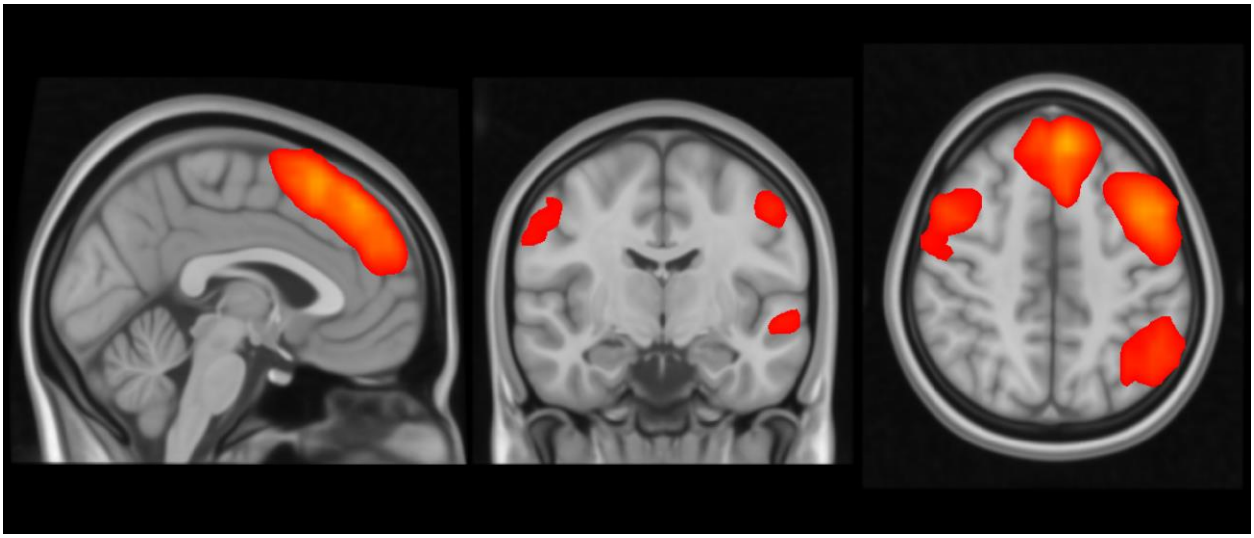
Other Components from gICA











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