Deconstructing Motivation Deficits
in Schizophrenia and Beyond

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Medical Science
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Abstract

Motivation deficits are a prevalent and pervasive symptom in schizophrenia, and are inextricably linked to poor functional outcomes in affected individuals. The primary objective of this thesis was to systematically deconstruct the multiple facets of the motivation system in schizophrenia and beyond. Our results revealed that reductions in self-reported pleasure in schizophrenia were primarily driven by patients with severe amotivation. Self-reported motivation deficits also predicted objective motivation task performance in a non-clinical sample, with no effect of schizotypal or depressive symptoms. Moreover, in a clinical sample of schizophrenia and major depressive disorder, our results identified a multi-faceted motivation framework consisting of five components, and two clusters of individuals characterized by differential behavioural motivation deficits. Taken together, our findings highlight the centrality of amotivation in schizophrenia and beyond, as well as the need to shift away from singular approaches, towards more comprehensive and dimensional investigations of the motivation system across disorders.
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My heart is so full. Love you all, endlessly.
Contributions

Chapter 3 (Study 1): Susana Da Silva and George Foussias designed the study, and Susana Da Silva led the statistical analyses and preparation of the first draft of the manuscript. Sarah Saperia and Ishraq Siddiqui contributed to the data collection and statistical analyses. Gagan Fervaha, Ofer Agid, Jeff Daskalakis, Arun Ravindran, Aristotle Voineskos, Konstantine Zakzanis, Gary Remington, and George Foussias reviewed and edited the manuscript, and provided feedback.

Chapter 4 (Study 2): George Foussias and Areti Apatsidou designed the study, and Susana Da Silva led the statistical analyses and preparation of the first draft of the manuscript. Areti Apatsidou, Sarah Saperia, and Ishraq Siddiqui contributed to the data collection and statistical analyses. Eliyas Jeffay, Aristotle Voineskos, Jeff Daskalakis, Gary Remington, Konstantine Zakzanis, and George Foussias reviewed and edited the manuscript, and provided feedback.

Chapter 5 (Study 3): Susana Da Silva and George Foussias designed the study, and Susana Da Silva led the statistical analyses and preparation of the first draft of the manuscript. Sarah Saperia and Ishraq Siddiqui contributed to the data collection and statistical analyses. Gagan Fervaha, Aristotle Voineskos, Jeff Daskalakis, Arun Ravindran, Konstantine Zakzanis, Gary Remington, and George Foussias reviewed and edited the manuscript, and provided feedback.
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
</tr>
<tr>
<td>AES-C</td>
<td>Apathy Evaluation Scale- Clinician version</td>
</tr>
<tr>
<td>AES-S</td>
<td>Apathy Evaluation Scale- Self-report</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>BACS</td>
<td>Brief Assessment of Cognition in Schizophrenia</td>
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<tr>
<td>BARS</td>
<td>Barnes Akathisia Rating Scale</td>
</tr>
<tr>
<td>BNA</td>
<td>Brief Neurocognitive Assessment</td>
</tr>
<tr>
<td>BSMSS</td>
<td>Barratt Simplified Measure of Social Status</td>
</tr>
<tr>
<td>CAMH</td>
<td>Centre for Addiction and Mental Health</td>
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<tr>
<td>CDSS</td>
<td>Calgary Depression Scale for Schizophrenia</td>
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<tr>
<td>CES-D</td>
<td>Centre for Epidemiologic Studies Depression Scale</td>
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<tr>
<td>CPZ</td>
<td>Chlorpromazine</td>
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<tr>
<td>CRRT</td>
<td>Cued-Reinforcement Reaction Time Task</td>
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<tr>
<td>DCT</td>
<td>Dot Counting Test</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorsolateral Prefrontal Cortex</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>DSM-IV-Text Revision</td>
</tr>
<tr>
<td>EEfRT</td>
<td>Effort Expenditure for Rewards Task</td>
</tr>
<tr>
<td>ERRT</td>
<td>Evoked and Representational Responding Task</td>
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<tr>
<td>HC</td>
<td>Healthy Control</td>
</tr>
<tr>
<td>HDRS</td>
<td>Hamilton Depression Rating Scale</td>
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<tr>
<td>IAPS</td>
<td>International Affective Picture System</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<td>-------------</td>
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<tr>
<td>IGT</td>
<td>Iowa Gambling Task</td>
</tr>
<tr>
<td>Kirby DD</td>
<td>Kirby Delay Discounting Task</td>
</tr>
<tr>
<td>MANOVA</td>
<td>Multivariate Analysis of Variance</td>
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<tr>
<td>MCT</td>
<td>Multitasking in the City Test</td>
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<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>NIMH</td>
<td>National Institute of Mental Health</td>
</tr>
<tr>
<td>OFC</td>
<td>Orbital Frontal Cortex</td>
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<td>PSS</td>
<td>Probabilistic Stimulus Selection Task</td>
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<tr>
<td>RDoC</td>
<td>Research Domain Criteria</td>
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<tr>
<td>SA</td>
<td>Schizoaffective Disorder</td>
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<tr>
<td>SANS</td>
<td>Scale for the Assessment of Negative Symptoms</td>
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<td>SAPS</td>
<td>Scale for the Assessment of Positive Symptoms</td>
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<tr>
<td>SAS</td>
<td>Simpson-Angus Scale</td>
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<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM-IV</td>
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<tr>
<td>SPQ</td>
<td>Schizotypal Personality Questionnaire</td>
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<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
</tr>
<tr>
<td>SZ</td>
<td>Schizophrenia</td>
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<tr>
<td>TEPS</td>
<td>Temporal Experience of Pleasure Scale</td>
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<tr>
<td>TEPS-Ant</td>
<td>Temporal Experience of Pleasure Scale-Anticipatory pleasure</td>
</tr>
<tr>
<td>TEPS-Con</td>
<td>Temporal Experience of Pleasure Scale-Consummatory pleasure</td>
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<tr>
<td>ViPR</td>
<td>Virtual Reality Progressive Ratio Task</td>
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Chapter 1

1. Introduction and Literature Review

1.1 Schizophrenia

1.1.1 History

Although the term “schizophrenia” has only been around for approximately 100 years, the clinical picture of the disease dates back to the 19th century as psychiatrists began documenting their descriptions of young patients presenting with various, progressively deteriorating symptoms with an unknown cause. Benedict Morel was one of the earliest physicians to use the term *demence precoce* (i.e. premature dementia) to describe these patients, while Arnold Pick used the Latin term *dementia praecox*. Other notable psychiatrists such as Karl Ludwig Kahlbaum, Ewald Hecker, and Thomas Clouston described similar clinical presentations using the terms “catatonia”, “hebephrenia”, and “adolescent insanity”, respectively (Clouston, 1904; Hecker, 1871; Jablensky, 2010; Kahlbaum, 1863; Morel, 1860). Informed by this work, it was Emil Kraepelin who first used the term *dementia praecox* (i.e. early dementia) to integrate these various clinical descriptions and define a single nosological entity caused by the deterioration of the psychic mind’s emotional, intellectual, and volitional processes in young adults, that was distinct from “manic-depressive insanity” (Berrios et al., 2003; Kraepelin, 1919). He further described the clinical presentation of the disease in terms of commonly observed symptoms such as attention and memory deficits, sensory hallucinations (e.g. auditory, visual), delusions (e.g. paranoia, ideas of reference), emotional dullness (e.g. indifference towards life and others) and volitional deterioration (e.g. lack of occupation/activity). Of note,
Kraepelin described a ubiquitous course of illness characterized by progressive deterioration, such that full recovery was unattainable for affected individuals. Further descriptions of this illness came from the works of Swiss psychiatrist, Eugen Bleuler. In 1911, Bleuler first coined the term schizophrenia (i.e. split mind), in reference to the distortions of reality associated with the disease (Bleuler, 1950). Recognizing the heterogeneity of the disease first noted by Kraepelin, Bleuler went on to describe a “group of schizophrenias” with slightly different prognoses and clinical manifestations. Ensuing work by Kurt Schneider led to the identification of 11 pathognomonic “first-rank symptoms” of schizophrenia which included audible thoughts, voices arguing or discussing, voices commenting on the patient’s actions, somatic passivity, thought withdrawal, thought insertion, thought broadcast, made feelings, impulses, and acts, and delusional perceptions (Carpenter and Strauss, 1974; Schneider, 1959). Along with the work of many other important figures, these contributions were pivotal in laying the foundation for a century of clinical research that continues to inform our understanding and conceptualization of schizophrenia.

1.1.2 Diagnosis, Epidemiology and Etiology

There are currently two established systems for classifying psychiatric illnesses: the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). The DSM-IV-TR diagnostic criteria for schizophrenia are outlined below (American Psychiatric Association, 2000), as these were the diagnostic criteria used in the studies that follow in this thesis. Of note, DSM-IV-TR has been recently updated to DSM-V, with only minimal changes to the schizophrenia module. Specifically, in
DSM-IV only one of the five key symptoms (i.e. delusions, hallucinations, disorganized speech, grossly disorganized behaviour, or negative symptoms) was required if bizarre delusions, or auditory hallucinations with running commentary or conversing voices were present. In DSM-V, however, this exception has been removed, and 2 of the 5 symptoms are required, one of which must be delusions, hallucinations or disorganized speech. Further, whereas in DSM-IV, negative symptoms included affective flattening, alogia, and avolition, in DSM-V, this was revised to avolition and diminished expression which reflects the current two-factor conceptualization of negative symptoms (American Psychiatric Association, 2013).

Table 1-1. DSM-IV-TR Diagnostic Criteria for Schizophrenia (American Psychiatric Association, 2000).

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

(1) delusions

(2) hallucinations

(3) disorganized speech (e.g., frequent derailment or incoherence)

(4) grossly disorganized or catatonic behavior

(5) negative symptoms, i.e., affective flattening, alogia, or avolition

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person’s
behavior or thoughts, or two or more voices conversing with each other.

B. **Social/occupational dysfunction:** For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal academic, or occupational achievement).

C. **Duration:** Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. **Schizoaffective and Mood Disorder exclusion:** Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred concurrently with the active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. **Substance/general medical condition exclusion:** The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
F. **Relationship to a Pervasive Developmental Disorder:** If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Schizophrenia affects approximately 1% of the global population, with average incidence rates of 15 per 100,000 per year (Saha et al., 2005; Tandon et al., 2008). Incidence rates are higher for males, individuals living in urban areas, individuals with a history of migration, and those with lower socio-economic status (McGrath et al., 2004; Tandon et al., 2008). Despite its relatively low prevalence compared to other mental illnesses, the personal, social, and economic burden of schizophrenia is among the highest, and has a tremendous impact on the individual, their family, and society as a whole (Chong et al., 2016; Goeree et al., 2005). The economic burden of schizophrenia can be attributed to both direct health care costs (i.e. hospitalizations), as well as unemployment and loss of productivity due to absenteeism and presenteeism (Chong et al., 2016). Schizophrenia is also linked to mortality rates that are two to three times higher than in the general population which is driven by greater premature deaths related to cardiovascular and metabolic problems, as well as elevated suicide rates (Saha et al., 2007). Moreover, the prevalence of concurrent disorders among individuals with schizophrenia is also higher than that of the general population. Specifically, patients with schizophrenia are three times more likely to develop an alcohol use disorder and five times more likely to develop a substance use disorder compared to the general population, further exacerbating poor health outcomes and mortality rates (Kessler et al., 1996). Psychiatric comorbidities are also common in schizophrenia patients, with
estimated rates of 15% for panic disorder, 29% for posttraumatic stress, 23% for obsessive compulsive disorder, and 50% for comorbid depression (Buckley et al., 2009). In addition to economic costs, and increased morbidity and mortality, patients often endure significant personal suffering, distress and poor quality of life, a personal burden that often extends to the family, as well (Knapp et al., 2004).

To date, there is no single known cause of schizophrenia. Instead, the combinations of genetic, environmental, and neurobiological mechanisms are thought to increase the risk of developing the disorder. Specifically, higher risks occur for individuals with a familial history of schizophrenia, particularly those with a first-degree relative with the disorder. Moreover, although combinations of specific genes and alleles that increase the risk for developing schizophrenia have been identified, there is no single gene whose expression causes the manifestation of the disorder. Additionally, environmental triggers such as stress and trauma may increase the likelihood of developing schizophrenia, especially for those with a genetic predisposition for the disorder. Other environmental factors include maternal infections or stress during pregnancy, birth during winter months or in urban areas, poor nutrition, and exposure to toxins or radiation (Tandon et al., 2008). Further, early and heavy cannabis use has been associated with a two-fold increase in the risk of developing schizophrenia, particularly in predisposed individuals (Arseneault et al., 2004).

One of the most enduring neurobiological explanations for the development of the disorder is the dopamine hypothesis, which suggests that schizophrenia occurs as a result of excess dopaminergic neurotransmission (Howes and Kapur, 2009). This hypothesis emerged with the discovery that antipsychotic medications exert their action through selective antagonism of dopamine D₂ receptors. Advances in the field, however, led to a
reconceptualization of this hypothesis to account for a region-specific cortical/subcortical dopaminergic dysfunction (Davis et al., 1991). Differential dopaminergic imbalances have also been linked to specific symptoms of schizophrenia, with positive symptoms related to an underlying cortical hyperdopaminergic state and negative symptoms associated with subcortical hypodopaminergia. Building on this work, Howes and Kapur (2009) broadened the scope of the dopamine hypothesis to highlight the importance of genetic and environmental interactions in dopamine dysregulation (Howes and Kapur, 2009).

Neuroimaging studies have also identified structural abnormalities associated with the disorder, such as enlarged ventricles, loss of gray matter, and reductions in temporal lobe structures including the hippocampus, amygdala, the superior temporal gyri, the prefrontal cortex, the thalamus, the anterior cingulate as well as white matter such as the corpus callosum (Keshavan et al., 2008). To date, however, there have not emerged specific neuroimaging-based abnormalities that are pathognomonic for schizophrenia.

1.1.3 Symptomatology and Course of Illness

Schizophrenia is a heterogeneous disorder characterized by prominent positive, negative, and cognitive symptoms. It should be noted, however, that not all symptoms are experienced by every individual, nor do they occur across all phases of the illness. For example, for many individuals, positive symptoms begin at first episode and resolve with treatment; however, many of the negative and cognitive symptoms predate the onset of frank psychosis, and persist throughout the course of the illness.
1.1.3.1 Positive Symptoms

The positive symptoms of schizophrenia are described as an excess or distortion of normal behavioural functions and perceptual processes. The development of frank psychotic symptoms marks formal onset of the first-episode of the disorder (Tandon et al., 2008). Specific examples of positive symptoms include sensory hallucinations (e.g. auditory, visual, tactile) and delusions (e.g. delusions of reference, grandiosity, thought broadcasting). Disorganized symptoms such as disorganized speech (e.g. derailment or loose associations) and disorganized or inappropriate behaviour are also common in individuals with schizophrenia, and often included within the clinical measures of positive symptoms. This constellation of symptoms is routinely evaluated in the commonly used clinical measures of positive and disorganized symptoms in schizophrenia, such as the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962).

1.1.3.2 Negative symptoms

Negative symptoms of schizophrenia are described as a reduction or absence of normal behaviour or experiences. Negative symptoms are often present in the prodromal phase of the disorder and persist throughout the course of the illness including remission, and cause substantial impairments to functioning in affected individuals (Foussias and Remington, 2010; Tandon et al., 2008). Examples of negative symptoms include anhedonia
(i.e. lack of interest or pleasure), affective flattening, apathy or amotivation, and alogia. Negative symptoms will be discussed in greater detail in Section 2 of this chapter.

One of the most widely used clinical measures of negative symptoms is the Scale for the Assessment of Negative Symptoms (SANS), which is comprised of 5 subscales: affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality, and inattention (Andreasen, 1982). Other measures include the Positive and Negative Syndrome Scale (PANSS), the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013), the Brief Negative Symptoms Scale (BNSS) (Kirkpatrick et al., 2011) and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962).

1.1.3.3 Cognitive symptoms

Cognitive impairment, another common feature of schizophrenia, is typically evident before the onset of the disorder and spans the course of the illness. Cognition has been classified into two domains: neurocognition and social cognition. Patients with schizophrenia demonstrate deficits in a wide range of neurocognitive domains including verbal memory, working memory, verbal fluency and executive functioning (Heinrichs and Zakzanis, 1998). Neurocognition is often assessed using neuropsychological tests such as the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004), and more recently, the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008).

Individuals with schizophrenia also demonstrate cognitive deficits in a variety of social domains including emotion perception, social perception, and theory of mind. Commonly used social cognition measures in schizophrenia include the Penn Emotion
Recognition Task (ER-40) to assess for emotion recognition, The Awareness of Social Inference Test (TASIT) for social perception, and the Reading the Mind in the Eyes Task (Baron-Cohen et al., 2001) for theory of mind.

1.1.3.4 Course of Illness

Schizophrenia is a disorder characterized by several distinct phases (An Der Heiden and Häfner, 2000; Tandon et al., 2009). During the prodromal phase of illness, patients often present with non-psychotic symptoms such as social withdrawal, diminished motivation, and cognitive impairments, followed by an exacerbation of positive symptoms (hallucinations, delusions, disorganized thinking/behaviour) in the acute phase, and eventually fall into the remission phase of the illness typically following treatment with antipsychotics, though residual symptoms (including positive, negative, and cognitive symptoms) remain for a sizeable number of patients (Tandon et al., 2009). Although positive symptoms are present to varying degrees of severity across phases, negative symptoms and poor functional outcomes persist for most individuals throughout the illness (Robinson et al., 2004).
Figure 1-1. Illustration of the course of schizophrenia with distinct phases, symptoms, and level of functioning outlined (Tandon et al., 2008).

1.1.4 Outcomes

Schizophrenia has long been characterized as a disorder with poor outcomes. Dating back to the early writings of Kraepelin, adequate long-term recovery, which he described as the ability to “live in freedom without difficulty, and to earn their living”, was only observed in approximately 13% of patients (Kraepelin, 1919). Over the past several decades, the definitions for recovery and remission have varied, with criteria ranging from symptom reduction to improvements in functional capabilities (Leucht and Lasser, 2006). One of the challenges in developing a formal definition for remission has been identifying criteria that conform to the heterogeneity of the disorder. The first consensus-based criteria for remission was proposed by the Remission in Schizophrenia Working Group (RSWG), and defined as a
severity score of mild or less on all psychotic, negative, and disorganized symptoms for a sustained period of 6 months (Andreasen et al., 2005). Longitudinal evaluations based on the RSWG criteria suggest that remission is attainable for a sizeable proportion of patients, with rates ranging between 17%-78% for first-episode patients and 16%-62% in chronic schizophrenia (AlAqeel and Margolese, 2012). Though considerably more optimistic than Kraepelin’s estimates, these rates are based on a definition of symptomatic remission that does not encompass functional recovery. This is a particularly important point to consider given the profound occupational, social, and interpersonal function impairments that persist beyond symptom remission (Abdallah et al., 2009; Bowie et al., 2008; Green et al., 2004). According to a World Health Organization study, for instance, only a small subset of individuals experienced favourable social adjustment outcomes across a 13 year period, with the majority demonstrating poor to fair outcomes (Mason et al., 1996). Thus, definitions of remission that rely on symptom amelioration alone may not reflect the reality of the enduring impairments experienced by individuals with schizophrenia. Indeed, longitudinal studies examining both symptom remission and functional recovery have reported substantially lower rates, with the majority of patients experiencing poor long-term outcomes (AlAqeel and Margolese, 2012; Kurihara et al., 2011; Mason et al., 1996; San et al., 2007; Valencia et al., 2015). For instance, in a study conducted by Robinson et al. (2004), only 13.7% of patients met criteria for full recovery lasting for a period of at least 2 years (Robinson et al., 2004), a number remarkably similar to Kraepelin’s observations in 1919. This has also been the case in the context of the recent large Danish OPUS early psychosis intervention trial, where only 14-17% of patients met criteria for recovery over the course of the first 10 years of illness, with approximately 60% of patients remaining symptomatic or institutionalized.
(Austin et al., 2013). Thus, despite significant advances in symptom treatment, recovery rates for schizophrenia have not improved considerably over the past 100 years.

1.1.5 Treatment

Since the fortuitous discovery of chlorpromazine in the 1950s, antipsychotic medications have represented the cornerstone of treatment for schizophrenia. Advances in psychopharmacology have since led to the modification and improvement of older generation drugs in an attempt to minimize the burden of side-effects. For instance, first generation or typical antipsychotics such as haloperidol and fluphenazine are associated with high incidence of extrapyramidal symptoms (EPS), tardive dyskinesia, and affective flattening. Though the mechanism of action remains dopaminergic in nature, specifically through antagonism at the $D_2$ receptor, atypical or second generation antipsychotics such as clozapine and olanzapine have a significantly lower risk of EPS. That being said, these newer generation drugs have been linked to metabolic side-effects including weight gain and diabetes (Newcomer, 2005). While both generations of antipsychotic medications have been equally effective at treating the positive symptoms of schizophrenia (with the exception of clozapine that has shown superiority to all other antipsychotic medications, particularly in treatment resistant populations), they have been less successful at treating the cognitive and negative symptoms of the illness (Jones et al., 2006; Keefe et al., 2007; Lieberman et al., 2005; McEvoy et al., 2006).
1.2 Negative Symptoms

1.2.1 History

The recognition of negative symptoms dates back to the early works of Kraepelin and Bleuler who observed a marked deterioration of volitional processes in individuals with schizophrenia (Bleuler, 1950; Kraepelin, 1919). The term “negative symptoms”, however, as well as its distinction from positive symptoms, was introduced in 1861 by John Russell Reynolds in the context of epilepsy (Berrios, 1985). Building on this work, and the ideas of Herbert Spencer regarding dissolution and evolution of the nervous system, John Hughlings Jackson introduced this concept into the field of psychiatry, describing negative symptoms as the dissolution of “neural arrangements”, and positive symptoms as the “release of lower levels from higher inhibitory control” (Jackson, 1958; Pearce, 2004).

The introduction of modern psychopharmacology in the 1950s led to an increase in emphasis on the treatment and assessment of positive symptoms. Ensuing work in the 1980s, however, led to the revival of interest in negative symptoms with the classification of symptom-based subtypes of schizophrenia, and more refined definitions of positive and negative symptoms (Andreasen and Olsen, 1982; Crow, 1985, 1980). The distinctiveness of negative symptoms was further elucidated by Carpenter et al. (1988), who differentiated between primary, idiopathic negative symptoms from the secondary negative symptoms that result from illness-related factors such as depression and medication side-effects (Carpenter et al., 1988). More recently, the positive-negative symptom dichotomy has been supported by a number of factor analytic studies. For instance, examinations of the SAPS and SANS have revealed 3-factor structures composed of positive, negative, and disorganized symptoms.
(Andreasen et al., 1995; Arndt et al., 1991; Grube et al., 1998), though not consistently, with one study identifying 11 factors (Peralta and Cuesta, 1999), and others reporting a five-factor model utilizing the PANSS (Nakaya et al., 1999; White et al., 1997). A consistent finding across studies, however, is the distinction of negative symptoms from other symptom domains of the disorder (Blanchard and Cohen, 2006).

1.2.2 The Negative Symptoms of Schizophrenia

Over the years, there has been considerable disagreement regarding the inclusion of specific symptoms within the domain of negative symptoms (Fenton and McGlashan, 1992). To this end, the National Institute of Mental Health (NIMH) released a consensus statement in 2005, with negative symptoms characterized as affective flattening (i.e. blunted or restricted affect), alogia (i.e. poverty of speech), avolition (i.e. apathy or amotivation), asociality, and anhedonia (i.e. diminished interest or pleasure). Moreover, symptoms such as attentional impairment, inappropriate affect, and poverty of content of speech, though included in traditional measures of negative symptoms (i.e. SANS), were excluded from the NIMH definition as they were found to be more closely related to the disorganized and cognitive symptoms of the disorder.

The underlying structure of negative symptoms has also been examined using factor and component analyses (Blanchard and Cohen, 2006). For instance, Keefe et al. (1992) conducted a confirmatory factor analysis using the SANS, and found three factors: diminished expression, social dysfunction, and disorganization (Keefe et al., 1992). Mueser et al. (1994) also proposed a 3-factor structure consisting of diminished expression,
inattention-alogia, and social amotivation (Mueser et al., 1994). However, in another study examining both medicated and non-medicated patients, Kelley et al. (1999) found a 2-factor solution comprised of affective flattening and diminished motivation (Kelley et al., 1999), a finding that has since been replicated by numerous studies (Kimhy et al., 2006; Malla et al., 2002; Messinger et al., 2011; Toomey et al., 1997). Accordingly, negative symptoms are currently conceptualized as two separate, but inter-related subdomains consisting of: 1) diminished expression (i.e. affective flattening, poverty of speech); and 2) amotivation (i.e. avolition/apathy and anhedonia/asociality) (American Psychiatric Association, 2013; Foussias and Remington, 2010; Kirkpatrick et al., 2006). Moreover, the two subdomains have been found to be differentially related to a number of clinical factors, with amotivation more consistently linked to poorer treatment, illness, and functional outcomes (Strauss et al., 2013). These findings have spurred interest into the specific symptoms of this subdomain, with a particular emphasis on anhedonia and amotivation.

Anhedonia has traditionally been considered a core symptom of schizophrenia, rooted in the findings from self-report measures such as the Chapman anhedonia scales which suggest a reduction in the ability to experience pleasure in these individuals (Chapman and Chapman, 1978; Horan et al., 2006a). However, the increasing concern regarding the construct validity of these measures, coupled with emerging objective investigations of pleasure, have called into question the true nature of the hedonic deficit in schizophrenia. Specifically, behavioural studies examining in-the-moment experience of pleasure across a number of sensory modalities have revealed comparable levels of pleasure between schizophrenia and healthy participants (Heerey and Gold, 2007; Trémeau et al., 2010). In line with the aforementioned studies, systematic reviews examining anhedonia in schizophrenia
have also revealed intact hedonic capacity in these individuals (Cohen and Minor, 2010; Llerena et al., 2012). Reflecting the discrepancies between subjective and objective measures of pleasure, the term “emotion paradox” has been used to describe anhedonia in schizophrenia. In an attempt to reconcile this paradox, anhedonia has been re-conceptualized as consummatory (“liking”) and anticipatory (“wanting”) pleasure. To this end, the Temporal Experience of Pleasure Scale (TEPS) was developed to distinguish between these two constructs. Studies utilizing the TEPS have revealed intact consummatory pleasure in schizophrenia but reductions in anticipatory pleasure (Favrod et al., 2009; Gard et al., 2007; Loas et al., 2009), though not consistently (Strauss et al., 2011). Taken together, these findings suggest that anhedonia, in its strictest definition, is not a core feature of schizophrenia. Indeed, a more recent review by Strauss and Gold (2012) has proposed that anhedonia, as it manifests itself in schizophrenia, should no longer be defined as a reduction in the capacity to experience pleasure, but rather as a “reduction in pleasure-seeking activities” and “beliefs of low pleasure” (Strauss and Gold, 2012).

In light of these findings, there has been a renewed interest in examining motivation deficits in schizophrenia. Amotivation has been consistently reported in individuals with schizophrenia using traditional measures of negative symptoms (i.e. the SANS), as well as the Apathy Evaluation Scale (AES) (Faerden et al., 2009; Foussias et al., 2011, 2009; Kiang et al., 2003). Moreover, motivation deficits are highly prevalent in schizophrenia, with estimated rates of approximately 30-50% (Evensen et al., 2012; Faerden et al., 2009). Closer examinations into the separate facets of motivation in schizophrenia have reaffirmed these findings, with studies revealing impairments in reward expectancy, reward valuation, reward learning, effort valuation and goal-directed decision making (Barch and Dowd, 2010; Kring...
and Barch, 2014). The multi-faceted motivation system will be discussed in greater detail in section 1.3.4.

1.2.3 Treatment of Negative Symptoms

Despite significant advances in treatment, negative symptoms have remained resistant to pharmacological interventions. While the introduction of second-generation antipsychotics appeared to offer promising results for treating negative symptoms, large clinical trials and meta-analyses have revealed inconsistent and modest effects, unlikely to be clinically significant (Harvey et al., 2016; Murphy et al., 2006; Remington et al., 2016). Given the clinical resemblance of negative symptoms and depression, the efficacy of anti-depressants has also been examined as potential treatment adjuncts. The results from these studies have been mixed, with one meta-analysis finding a positive effect (Helfer et al., 2016; Singh et al., 2010), but most lacking evidence for the efficacy of anti-depressant augmentation in the treatment of negative symptoms (Fusar-Poli et al., 2015; Remington et al., 2016; Rummel et al., 2006; Sepehry et al., 2007). Further, stimulants, glutamatergic, and cholinergic agents have also been evaluated as adjunct to antipsychotics, with similar modest and inconsistent benefits (Arango et al., 2013; Buchanan et al., 2007; Singh and Singh, 2011).

Beyond pharmacological interventions, more recent investigations have explored brain stimulation therapies for negative symptoms. Repetitive transcranial magnetic stimulation (rTMS), for instance, has demonstrated some efficacy at high frequencies (Goyal et al., 2007; Hajak et al., 2004; Prikryl et al., 2007; Schneider et al., 2008), though not consistently (Holi et al., 2004; Mogg et al., 2007; Novák et al., 2006). Further, evidence from
a more recent multicenter randomized controlled trial revealed no significant benefit of rTMS for negative symptoms (Wobrock et al., 2015). Additionally, the use of transcranial direct current stimulation (tDCS) has revealed some promising findings, with a few studies demonstrating beneficial effects (Agarwal et al., 2013; Brunelin et al., 2012; Gomes et al., 2015).

Psychosocial strategies have also been examined as potential treatments for negative symptoms in schizophrenia, with the focus primarily on cognitive behavioural therapy. Though there have been some positive findings (Sensky et al., 2000), recent meta-analyses have again revealed only modest benefits for negative symptoms (Jauhar et al., 2014; Jones et al., 2012; Klingberg et al., 2011). Moreover, other psychosocial treatments such as family therapy, assertive community treatment, social skills training, and cognitive remediation have also offered minimal positive benefits beyond the primary outcomes that they were developed to target (Bustillo et al., 2001; Pilling et al., 2002).

In the largest and most extensive meta-analysis of existing treatments for negative symptoms to date, Fusar-Poli et al. (2015) examined the efficacy of typical and atypical antipsychotics, antidepressants, glutamatergic medications, combinations of pharmacological agents, brain stimulation, and psychological interventions. The results of this study revealed only small to moderate effect sizes for the majority of these interventions, with none demonstrating clinically meaningful improvements (Fusar-Poli et al., 2015). Taken together, these findings highlight that negative symptoms continue to represent an unmet therapeutic need in the treatment of schizophrenia.
1.2.4 Negative Symptoms and Functional Outcome

Schizophrenia has long been characterized as a disorder with poor functional outcomes. Amongst the multitude of debilitating symptoms, negative symptoms have been identified as one of the most reliable predictors of functional deficits, above and beyond the influence of positive, disorganized and depressive symptoms (Fenton and McGlashan, 1991; Ho et al., 1998; Kiang et al., 2003; Rabinowitz et al., 2012). Indeed, studies have consistently shown a strong association between severity of negative symptoms and poor social, community and vocational functioning, as well as low quality of life (Evensen et al., 2012; Faerden et al., 2009; Fervaha et al., 2014a). Within the broader construct of negative symptoms, important findings have also emerged regarding the influence of specific subdomains on functional outcomes. In terms of diminished expression, for instance, some studies have demonstrated a significant correlation with functioning (Gur et al., 2006; Kring et al., 2013), however most have failed to replicate these results (Chang et al., 2017; Fervaha et al., 2013b; Foussias et al., 2009; Green et al., 2012; Salem and Kring, 1999; Sayers et al., 1996; Strauss et al., 2013). In contrast, the amotivation subdomain has been consistently shown to predict poor functional outcomes in schizophrenia (Faerden et al., 2009; Foussias et al., 2009; Konstantakopoulos et al., 2011).

Within the amotivation subdomain, anhedonia has demonstrated a significant relationship with occupational and social functioning (Blanchard et al., 1998; Herbener et al., 2005), though not consistently (Katsanis et al., 1992; Strauss et al., 2011). The nature of this relation is complicated by the recent reconceptualization of anhedonia in schizophrenia as reductions in pleasure-seeking activities, along with beliefs of low pleasure, rather than a reduced capacity for pleasure (Strauss and Gold, 2014). Thus, it is difficult to determine the
extent to which the relationship between anhedonia and functioning is driven by a true hedonic impairment.

Motivation deficits have been consistently highlighted as a core feature of schizophrenia, especially in terms of its link to poor functioning (Fervaha et al., 2013b; Foussias et al., 2009). Specifically, it has been posited that amotivation represents the most reliable predictor of poor functional outcomes in first-episode and chronic schizophrenia, both cross-sectionally and longitudinally (Faerden et al., 2009; Fervaha et al., 2014b; Foussias et al., 2009). Indeed, studies have revealed that motivation deficits account for up to 70% of the variance in community and psychosocial functioning, with no significant contribution from other symptoms (Foussias et al., 2009; Kiang et al., 2003; Konstantakopoulos et al., 2011).

Neurocognition has also been examined in the context of functional outcomes, with studies revealing significant relationships between functional disability and cognitive impairments in domains such as verbal memory, working memory, and executive functioning (Green, 1996; Green et al., 2004; Milev et al., 2005), though not consistently (Addington and Addington, 1999; Foussias et al., 2009; Konstantakopoulos et al., 2011; Norman et al., 1999). The relationship between cognition and functioning is also complicated given the overlap in variance accounted for by negative symptoms and cognition (Milev et al., 2005), with motivation deficits partially mediating the relationship between cognition and functioning (Foussias et al., 2015; Gard et al., 2009; Nakagami et al., 2008; Ventura et al., 2009).
In summary, the existing literature on negative symptoms highlights the prevalence of amotivation in schizophrenia, a symptom that is inextricably linked to poor functional outcomes, all the while representing an unmet therapeutic need.

1.3 Motivation

1.3.1 Motivation – a Definition

Motivation, the ability to initiate and/or sustain goal-directed behaviour, is a multi-faceted system, consisting of a number of interrelated reward processes. Current conceptualizations of motivation outline a framework whereby 1) hedonic capacity (i.e. “liking”) and 2) reward expectancy (i.e. “wanting”, established through appropriate reward learning) converge to inform both 3) reward valuation and effort valuation (i.e. cost-benefit analysis), followed by 4) the development and execution of an action plan to achieve the desired outcome (Figure 1-2) (Barch and Dowd, 2010). This framework aligns well with the construct of approach motivation outlined by the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) within the Positive Valence Systems, which similarly outlines a multi-faceted construct consisting of reward valuation, effort valuation/willingness to work, reward expectancy, action-selection/preference-based directed decision making, initial and sustained responsiveness to reward, and reward learning (Cuthbert and Insel, 2013).
1.3.2 Motivation Deficits across Disorders

The inclusion of motivation within the RDoC Positive Valence System highlights the prevalence and clinical relevance of motivation deficits, and solidifies its designation as a core aspect of psychopathology that cuts across diagnostic boundaries (Cuthbert and Insel, 2010). Indeed, motivation deficits are prevalent across a number of neuropsychiatric and neurologic illnesses beyond schizophrenia, including major depressive disorder (MDD), Parkinson’s disease, Alzheimer’s disease, and Huntington’s disease (Brown and Pluck, 2000; Levy et al., 1998; Marin et al., 1991; Pluck and Brown, 2002; Robert et al., 2009; Starkstein
and Brockman, 2011). In the context of schizophrenia, the motivational deficits associated with depression are perhaps the most relevant given the phenomenological symptom overlap between negative symptoms and depression. Indeed, a major challenge in the assessment and treatment of schizophrenia has been differentiating negative symptoms from depression (Addington et al., 1994, 1990; Collins et al., 1996). Thus, examining motivation deficits in major depressive disorder may serve to elucidate common underlying mechanisms driving these impairments across disorders, and aligns well with emerging dimensional approaches to understanding psychopathology (Cuthbert and Insel, 2010).

1.3.3 Motivation Deficits in Major Depressive Disorder

Major depressive disorder is one of the most common mental illnesses, with a lifetime prevalence of approximately 11% in Canada (Patten et al., 2009). Moreover, it is considered one of the leading causes of disability in the world (World Health Organization, 2017). In addition to the personal distress and poor quality of life often experienced by affected individuals, depression is also associated with a tremendous economic burden driven by loss of productivity in the form of both presenteeism and absenteeism (Lerner et al., 2004; Patten et al., 2009).

According to the DSM, there are 9 diagnostic symptoms of MDD: depressed mood; anhedonia (i.e. loss of interest or pleasure); weight/appetite changes; insomnia/hypersomnia; motor retardation/agitation; loss of energy; concentration impairments; worthlessness/inappropriate guilt; and suicidality (American Psychiatric Association, 2000). In order to meet criteria for MDD, an individual must endorse 5 out of the 9 symptoms, one
of which being depressed mood or anhedonia. However, the diagnostic criterion does not distinguish between the hedonic (i.e. loss of pleasure) and motivational (i.e. loss of interest/drive) components of anhedonia. Although anhedonia in MDD is traditionally viewed as a reduction in pleasure, recent examinations have revealed important distinctions between consummatory (“liking”) and anticipatory (“wanting”) pleasure, with the latter more closely related to motivational processes (Klein, 1984). Accordingly, anhedonia has been positioned as a facet within the broader motivational framework (Treadway and Zald, 2011). This fits well with the results of a study examining the strength of non-diagnostic criteria in predicting an MDD diagnosis. Specifically, with the exception of depressed mood, amotivation (i.e. diminished drive and interest) outperformed all other existing criteria in distinguishing MDD from non-MDD (McGlinchey et al., 2006; Zimmerman et al., 2006). Motivation deficits have similarly emerged as determinants of poor functional outcomes in MDD, as well as predictors of treatment and illness outcomes, above and beyond the effects of depressed mood (Fervaha et al., 2016b; Uher et al., 2012; Wells et al., 1989). Furthermore, in a study conducted by Lam et al. (2012), lack of motivation was endorsed by 93% of the sample, and ranked as the symptom most interfering with work functioning (Lam et al., 2012). Amotivation is also one of the most commonly endorsed residual symptoms of depression (Fava et al., 2014).
1.3.4 The Multiple Facets of Motivation in Schizophrenia and Major Depressive Disorder

Informed by the work of Barch and Dowd (2010), the ensuing studies presented in this thesis focus on four major components of the reward and motivation system: hedonics or liking, reward expectancy and wanting, cost-benefit decision making (i.e. value representation and cost computation), and goal-directed decision making.

1.3.4.1 Hedonics

Hedonic capacity, the ability to experience pleasure in response to a positive stimulus, has been extensively examined in both schizophrenia and major depressive disorder. The impetus for examining hedonic capacity in schizophrenia has been grounded in the long-held assumption that motivation deficits were driven by reductions in pleasure in these individuals. However, this assumption has been recently challenged by studies utilizing self-report questionnaires (i.e. TEPS), as well as objective measures of hedonic capacity which have revealed intact in-the-moment experience of pleasure (i.e. “liking”) (Cohen and Minor, 2010; Gard et al., 2007; Kring and Moran, 2008; Llerena et al., 2012; Yan et al., 2012). In line with the aforementioned findings, some neuroimaging studies have revealed intact ventral striatal activation during reward receipt in patients with schizophrenia (Kirsch et al., 2007; Mucci et al., 2015; Simon et al., 2010), though not consistently (Barch and Dowd, 2010). Moreover, studies have reported reduced activation in other relevant regions such as the insula, orbital frontal cortex (OFC), medial frontal cortex and amygdala (Barch and Dowd, 2010; Plailly et al., 2006; Schneider et al., 2007). Importantly, however, the evidence
for intact reward responsiveness in schizophrenia is supported by findings suggesting that hedonic deficits are not mediated by dopamine hypofunction, but rather by an opiodic or serotonergic system in the nucleus accumbens, ventral pallidum and OFC (Barch and Dowd, 2010; Berridge, 2007; Smith and Berridge, 2007, 2005).

Research on motivation deficits in depression has been primarily focused on hedonic capacity, with most studies utilizing traditional self-report questionnaires, such as the Chapman scales for physical and social anhedonia (Horan et al., 2006b). Though these scales have consistently revealed a hedonic impairment in depression, they do not distinguish between the consummatory and anticipatory aspects of anhedonia (Klein, 1984). Unfortunately, studies utilizing the TEPS in depressed samples are limited, with a single study suggesting deficits in both consummatory and anticipatory pleasure compared to healthy controls (Liu et al., 2011). Moreover, behavioural examinations of reward responsiveness have been inconsistent, with some studies revealing that MDD patients rate positive stimuli as less pleasant and arousing than healthy controls (Berenbaum and Oltmanns, 1992; Dunn et al., 2004), but others failing to replicate these findings (Dichter et al., 2004; Gehricke and Shapiro, 2000; Keedwell et al., 2005). A meta-analysis conducted by Bylsma et al. (2008) revealed a reduction in emotional responsiveness to both positive and negative valence stimuli in MDD (Bylsma et al., 2008). Hedonic capacity has also been examined using a signal detection paradigm, with response bias as a behavioural proxy for responsiveness to reward. The results from these studies have revealed reduced reward responsiveness in MDD, such that patients fail to modulate their behaviour towards the more rewarding stimulus (Henriques et al., 1994; Pizzagalli et al., 2009, 2008). That being said, these tasks are contingent on the participant’s ability to learn about the most rewarding
stimulus, and may therefore be more indicative of impairments in reward learning (Rizvi et al., 2016). In terms of the neurobiological mechanisms underlying reward responsiveness in MDD, functional magnetic resonance imaging (fMRI) studies have consistently shown reduced striatal responses to rewards in depressed individuals, which was correlated with elevated levels of anhedonia (McCabe et al., 2009; Smoski et al., 2009).

1.3.4.2 Reward Expectancy

Reward expectancy refers to the anticipation and expectation of future rewards, the processes underlying a sense of “wanting”. To date, there have been limited behavioural studies examining reward expectancy in schizophrenia. These studies, which have relied on reinforcement-related speeding tasks, suggest reward anticipation deficits in SZ, such that patients exhibit reduced speeding in response to rewarding cues compared to healthy controls (Mann et al., 2013; Murray et al., 2008; Waltz et al., 2010), though not consistently (Roiser et al., 2009). In another study by Heerey et al. (2007), patients with schizophrenia demonstrated impairments in generating behaviour in response to an internal representation of an evocative stimulus, despite intact hedonic capacity. Most research on reward expectancy in schizophrenia has focused on neuroimaging, with evidence of reduced ventral striatum activation in response to reward-predicting cues in both medicated and non-medicated individuals (Barch and Dowd, 2010; Juckel et al., 2006b; Schlagenhauf et al., 2008, 2014; Simon et al., 2015). Importantly, these reductions were correlated with severity of negative symptoms, as well as amotivation specifically (Juckel et al., 2006b, 2006a; Simon et al., 2010). Further, Juckel et al. (2006) revealed differential reward system
Impairments in patients treated with typical versus atypical antipsychotics, with only the former demonstrating impairments in reward anticipation (Juckel et al., 2006b). Of note, there is an important learning component to reward expectancy, such that an individual must be able to learn the appropriate cues associated with a reward in order to appropriately predict that it will be rewarding in the future. Behavioural studies examining reward learning in SZ have revealed impairments in rapid reward learning, but intact gradual or habitual learning (Strauss et al., 2014; Waltz et al., 2011, 2007). Moreover, there is evidence for specific reward-driven reinforcement learning deficits, but spared punishment-driven learning (Gold et al., 2012; Waltz et al., 2007), though some studies have also found impairments in learning from punishment (Fervaha et al., 2013a). Reinforcement learning deficits are thought to be mediated by similar abnormal dopaminergic striatal responses related to reward anticipation (Barch et al., 2016), as well as dysfunctions in the connection between basal ganglia and orbitofrontal cortex regions of the brain (Barch and Dowd, 2010; Frank et al., 2004; Frank and Claus, 2006).

Research on reward expectancy in major depressive disorder is limited, though there is some evidence to suggest that patients with MDD also fail to modulate behaviour in response to cued rewards (Pizzagalli et al., 2009). Findings from neuroimaging studies in MDD have been inconsistent, with some studies showing reduced striatal activation in response to anticipation cues (Forbes et al., 2009; Smoski et al., 2009; Stoy et al., 2012), but not others (Gorka et al., 2014; Knutson et al., 2008). Reward learning has been extensively examined in MDD, with consistent findings indicating that patients are impaired in the ability to utilize feedback or reinforcement to guide behaviour (Henriques and Davidson, 2000; Pizzagalli et al., 2008; Vrieze et al., 2013). Specifically, these impairments have been linked
to abnormal responses to negative feedback as well as a reduction in responsiveness to reward (Eshel and Roiser, 2010). Reward learning deficits have also been extended to dysphoric individuals (Henriques et al., 1994; Pizzagalli et al., 2005) and remitted MDD patients (Pechtel et al., 2013).

1.3.4.3 Cost-Benefit Decision Making

Cost-benefit decision making refers to the process by which reward value (i.e. reward representation) is integrated and weighed against the effort required (i.e. effort computations) to pursue and achieve a desired goal.

1.3.4.3.1 Value Representation

Value representation (i.e. reward valuation) refers to the process in which a prospective reward is appraised according to prior experiences and learning, and subsequently assigned value. Typically, reward valuation is investigated using discounting paradigms, which measure participants’ preferences for reward depending on the magnitude, delay and probability of receiving the reward. On the Kirby Delay Discounting task for instance, individuals with schizophrenia demonstrate steeper discounting rates compared to healthy controls, particularly for larger delayed rewards (Ahn et al., 2011; Avsar et al., 2013; Heerey et al., 2011, 2007; Weller et al., 2014; Yu et al., 2017). Evidence for impaired reward valuation in schizophrenia has also emerged from probabilistic choice tasks, suggesting that patients undervalue potential losses when weighting options with differing win-loss
probabilities (Heerey et al., 2008). Neurobiological investigations of reward valuation have been limited in SZ, with suggested links to lateral and medial orbitofrontal cortex functions (Barch and Dowd, 2010; Gold et al., 2008), as well as to the amygdala, striatum, midbrain, and ventromedial prefrontal cortex (Lawrence et al., 2011).

MDD participants have also demonstrated impairments in reward valuation, showing a preference for smaller immediate rewards over the larger and more beneficial, delayed reward on the Kirby Delay Discounting Task (Dombrovski et al., 2012; Pulcu et al., 2014; Takahashi et al., 2008). In contrast, a recent study utilizing a probability choice task independent of learning requirements found that patients with MDD exhibit intact reward valuation during decision-making (Chung et al., 2017).

1.3.4.4 Effort Computation

Effort computation refers to the process of weighing the cost and benefit of a desired outcome, which translates into one’s willingness to exert effort. Most behavioural studies examining effort valuation in schizophrenia have utilized an effort-based decision making paradigm. Studies utilizing the Effort Expenditure for Rewards Task (EEfRT), for instance, have consistently revealed reductions in SZ patients’ willingness to exert effort for high reward-high probability conditions. Interestingly, these findings have suggested that SZ patients do not demonstrate reductions in their overall expenditure of effort, but rather, exhibit inefficient allocation of effort across different probability and reward conditions (Barch et al., 2014; Fervaha et al., 2013d; Gold et al., 2013; Treadway et al., 2015). Of note, the number of effortful task selections was correlated with severity of negative symptoms.
(Gold et al., 2013) and amotivation (Fervaha et al., 2013d) in these studies. Effort valuation has also been assessed using the Virtual Reality Progressive Ratio (ViPR) task, an ecologically valid measure developed by our own group, which couples a progressive ratio paradigm with virtual reality. Results from this task similarly reveal that patients with SZ demonstrate a reduced willingness to work in the face of increasing effort requirements (Foussias et al., 2013).

Research examining effort valuation in MDD using the EEfRT have also shown a reduction in patients’ willingness to expend effort for greater monetary gains (Treadway et al., 2012; Yang et al., 2016), although one study failed to replicate these findings (Sherdell et al., 2012). Furthermore, a study conducted by Hershenberg et al. (2016) examining effort using a progressive ratio task revealed reduced motivation in both unipolar and bipolar depression (Hershenberg et al., 2016).

The neurobiological mechanisms underlying effort valuation have been given much less attention, though there is evidence for a dopaminergic role in motivated behaviour, particularly in the nucleus accumbens. This hypothesis is consistent with animal studies demonstrating effort reductions in dopamine depleted rats (Hauber and Sommer, 2009; Salamone et al., 2005, 2003). Further, the anterior cingulate cortex (ACC) has also been implicated in the physical processing of effort-cost computations (Walton et al., 2003).

1.3.4.5 Goal-Directed Decision Making

Goal-directed decision making refers to the process of planning, and optimizing choice selection in pursuit of a desired outcome. Decision-making has been extensively
examined in schizophrenia, with the majority of studies utilizing the Iowa Gambling Task (IGT) (Bechara et al., 1994; Sevy et al., 2007). These findings have suggested impaired decision-making, such that SZ patients make significantly more disadvantageous choices compared to healthy controls (Beninger et al., 2003; Kester et al., 2006; Premkumar et al., 2008; Ritter et al., 2004; Shurman et al., 2005), though not consistently (Cavallaro et al., 2003; Evans et al., 2005; Rodriguez-Sánchez et al., 2005; Wilder et al., 1998). Furthermore, a study examining real-world executive functioning in a natural environment revealed that patients with schizophrenia committed more omission and commission errors while completing activities of daily living (Semkovska et al., 2004). Work from our group has similarly demonstrated impairments in goal-directed decision making in SZ using the Multi-tasking in the City Test (MCT), a goal planning and action task in a virtual environment (Jovanovski et al., 2012; Siddiqui et al., 2015). Neuroimaging studies have consistently linked decision-making and executive functioning to the DLPFC, with findings of reduced DLPFC activation in patients with schizophrenia (Glahn et al., 2005; Minzenberg et al., 2009).

Goal-directed decision making has received considerably less attention in depression with some studies revealing impairments on the IGT (Cella et al., 2010; Must et al., 2006; Smoski et al., 2008), but others finding intact performance (Dalgleish, 2004; Gorlyn et al., 2013; Han et al., 2012). Interestingly, one study noted enhanced performance in MDD patients, such that they made significantly fewer disadvantageous choices than healthy controls. Though somewhat unexpected, these findings are consistent with the hypothesis that depression is associated with a heightened aversion to negative feedback (Smoski et al., 2008).
Chapter 2: Overview of experiments and hypotheses

This thesis contains chapters comprised of three manuscripts, each designed to advance our understanding of motivation deficits in schizophrenia and beyond. Study 1 (Chapter 3) has been published in Psychiatry Research. Study 2 (Chapter 4) and study 3 (Chapter 5) will be submitted for publication in peer-reviewed journals. The rationale and hypotheses for each study are outlined below.

2.1 Study 1: Investigating consummatory and anticipatory pleasure across motivation deficits in schizophrenia and healthy controls

2.1.1 Background

Anhedonia has long been considered a core feature of schizophrenia; however this notion has recently been challenged. Drawing from the depression literature, anhedonia has been reconceptualized, and subsequently examined in terms of both consummatory and anticipatory pleasure. These studies have revealed reduced anticipatory pleasure, but intact consummatory pleasure, though this finding has not been consistent. Thus, the true nature of anhedonia in schizophrenia remains elusive. In order to better understand this phenomenon, the aim of the present study was to examine consummatory and anticipatory pleasure in a large sample of schizophrenia patients and healthy controls. Further, given the role of hedonic capacity within the larger motivation framework, we also sought to investigate consummatory and anticipatory pleasure across a spectrum of motivation deficits.
2.1.2 Hypotheses

We hypothesized that patients with schizophrenia would demonstrate a reduction in anticipatory pleasure, but intact consummatory pleasure. Further, we hypothesized that anticipatory pleasure deficits would be related to the severity of clinical amotivation.

2.2 Study 2: An examination of the multi-faceted motivation system in healthy young adults: the impact of schizotypal, depressive and amotivation symptoms

2.2.1 Background

Motivation is conceptualized as a complex multi-faceted system; however, the existing literature primarily consists of individual studies examining isolated facets of motivation in schizophrenia and depression. Moreover, our understanding of these deficits is further complicated by inconsistent findings that have been attributed to illness-related factors such as medication effects and cognitive dysfunction. Thus, in order to minimize the effects of these confounds, the present study aimed to comprehensively examine the motivation framework as it relates to schizotypy, depressive symptoms, and amotivation in a non-clinical sample.

2.2.3 Hypotheses

We hypothesized that higher levels of amotivation would be related to poorer task performance across all facets of motivation. We also hypothesized that individuals with higher schizotypal traits would be impaired in reward expectancy and effort valuation,
whereas more severe depressive symptoms would be related to impairments in reward responsiveness and reward valuation.

### 2.3 Study 3: A dimensional examination of motivation system impairments in schizophrenia and major depressive disorder

#### 2.2.1 Background

Amotivation is a highly prevalent symptom in both schizophrenia and major depressive disorder, and has been linked to poor functional outcomes in affected individuals. To this end, motivation has been recognized as a fundamental construct of human behaviour, operationalized as a multi-faceted system comprised of hedonic capacity, reward expectancy, reward valuation, effort valuation, and goal-directed decision making. The research to date, however, is limited by studies focusing on discrete facets of motivation within single illness populations, which ultimately lack the ability to delineate specific processes underlying clinical amotivation across disorders. Thus, the present study aimed to systematically deconstruct the multi-faceted motivation framework in schizophrenia, major depressive disorder, and healthy control participants. In light of emerging dimensional approaches to examining psychopathology, we also sought to identify clusters of individuals with similar motivation deficit profiles across diagnostic categories. To our knowledge, this is the first study to comprehensively examine the motivation framework using objective computerized tasks concurrently in schizophrenia and major depressive disorder.
2.2.2 Hypotheses

We hypothesized that the motivation framework would be comprised of 5 facets: hedonic capacity, reward expectancy and learning, reward valuation, effort valuation, and goal-directed decision making. Further, we hypothesized that amotivation would drive reward processing impairments, regardless of diagnostic status.
Chapter 3: Investigating consummatory and anticipatory pleasure across motivation deficits in schizophrenia and healthy controls

Contents of this chapter have been published as:


Investigating consummatory and anticipatory pleasure across motivation deficits in schizophrenia and healthy controls


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3.1 Abstract

Anhedonia has traditionally been considered a characteristic feature of schizophrenia, but the true nature of this deficit remains elusive. This study sought to investigate consummatory and anticipatory pleasure as it relates to motivation deficits. Eighty-four outpatients with schizophrenia and 81 healthy controls were administered the Temporal Experience of Pleasure Scale (TEPS), as well as a battery of clinical and cognitive assessments. Multivariate analyses of variance were used to examine the experience of pleasure as a function of diagnosis, and across levels of motivation deficits (i.e. low vs. moderate. vs. high) in schizophrenia. Hierarchical regression analyses were also conducted to evaluate the predictive value of amotivation in relation to the TEPS. There were no significant differences between schizophrenia and healthy control groups for either consummatory or anticipatory pleasure. Within the schizophrenia patients, only those with high levels of amotivation were significantly impaired in consummatory and anticipatory pleasure compared to low and moderate groups, and compared to healthy controls. Further, our results revealed that amotivation significantly predicts both consummatory and anticipatory pleasure, with no independent contribution of group. Utilizing study samples with a wide range of motivation deficits and incorporating objective paradigms may provide a more comprehensive understanding of hedonic deficits.
3.2 Introduction

Anhedonia, or the diminished capacity to experience pleasure, has traditionally been considered a core negative symptom in schizophrenia that is linked to poor functional outcomes in these individuals. The recognition of anhedonia in schizophrenia dates back to the early works of Kraepelin and Bleuler who observed a marked emotional indifference in this population (Bleuler, 1950; Kraepelin, 1919). Seeking to replicate this finding quantitatively, questionnaires such as the Chapman Physical Anhedonia Scale were developed to measure participants’ self-reported levels of pleasure (Chapman and Chapman, 1978). In line with Kraepelin and Bleuler’s observations, findings from these reports found that patients with schizophrenia endorsed deficits in hedonic experience.

Rating one’s level of pleasure, however, does not necessarily measure one’s objective capacity for experiencing pleasure, particularly when this involves the subjective reporting of non-current feelings and emotional experiences (Strauss and Gold, 2012). For example, when asked to reflect on, and rate the extent to which a stimulus or event is pleasurable, participants with schizophrenia report significantly lower levels of pleasure compared to healthy controls (Blanchard et al., 1998; Herbener and Harrow, 2002; Horan et al., 2006a). In contrast, when patients are actively exposed to emotionally evocative stimuli, they report experiencing pleasure to the same degree as healthy controls (Cohen and Minor, 2010; Llerena et al., 2012; Yan et al., 2012). These contradictory findings have raised questions regarding the construct validity of previous self-report ratings of anhedonia (Germans and Kring, 2000; Leventhal et al., 2006).
In an attempt to further understand hedonic experience in schizophrenia, the Temporal Experience of Pleasure Scale (TEPS) was developed (Gard et al., 2006). The TEPS builds on previous efforts in depression to differentiate between consummatory and anticipatory experiences of pleasure (Klein, 1984). Consummatory pleasure refers to a state of liking or enjoying a stimulus at the moment of exposure, while anticipatory pleasure refers to the experience of wanting a stimulus in anticipation of a future reward or pleasurable experience (Klein, 1984). Many studies utilizing the TEPS have found comparable levels of consummatory pleasure between schizophrenia participants and healthy controls, which is in keeping with experiential laboratory-based findings (Chan et al., 2010; Favrod et al., 2009; Gard et al., 2007; Heerey and Gold, 2007; Loas et al., 2009; Trémeau et al., 2010). In contrast, these studies have found that individuals with schizophrenia experience reduced anticipatory pleasure compared to healthy controls. However, this has not been consistent across all studies using the TEPS, with a more recent study finding the opposite: differences in consummatory pleasure, but intact anticipatory pleasure (Strauss et al., 2011). Thus, the true nature of the hedonic deficit in schizophrenia remains elusive.

Hedonic impairments in schizophrenia comprise one facet of the broader construct of motivation deficits, and figure prominently within the negative symptoms of the illness, along with other clinical symptoms such as avolition and apathy (Foussias and Remington, 2010). Recent frameworks for characterizing the human motivation system have positioned both consummatory pleasure (i.e., liking) and anticipatory pleasure (i.e., wanting) as key elements that serve to inform goal-directed behaviour (Barch and Dowd, 2010). That is, if an individual can neither appreciate or enjoy a pleasurable experience in the moment, nor
foresee the value of a pleasurable reward in the future, they may be less likely to pursue it, thus contributing to the clinical manifestation of motivation deficits (Kring and Barch, 2014). With such clinical motivation deficits being repeatedly linked to poor functional outcomes in schizophrenia (Fervaha et al., 2014b; Fervaha et al., 2015a; Foussias et al., 2009; Green et al., 2012; Konstantakopoulos et al., 2011), clarifying the nature and extent of hedonic impairments in affected individuals is particularly important.

In the present study, we sought to examine consummatory and anticipatory pleasure in a large sample of schizophrenia and healthy control participants. Given the role of hedonic capacity within the larger motivation framework, we also sought to investigate differences in consummatory and anticipatory pleasure across a spectrum of motivation deficits in schizophrenia, in order to ascertain the influence of amotivation on the experience of pleasure. We hypothesized that participants with schizophrenia would exhibit significantly lower levels of anticipatory pleasure compared to healthy participants, but no differences in consummatory pleasure. We also hypothesized that impaired anticipatory pleasure would be related to more severe amotivation for patients with schizophrenia.

3.3 Methods & Materials

3.3.1 Participants

Participants recruited for this study consisted of 84 patients with schizophrenia (SZ) and 81 healthy controls (HC) matched for age and sex. Participants in the SZ group were between 18 and 55 years of age with a DSM-IV diagnosis of SZ or schizoaffective (SA) disorder, determined through structured diagnostic interviews (Structured Clinical Interview
for DSM-IV Axis I Disorders for 57 participants; Mini International Neuropsychiatric Interview for 108 participants) (First et al., 1997; Sheehan et al., 1998). All SZ participants were outpatients on a stable dose of antipsychotic medication for at least four weeks; were capable to consent to treatment; and were fluent in English. SZ participants were excluded if they met diagnostic criteria for any other Axis I disorder; had a history of substance abuse or dependence in the past 6 months (with the exception of nicotine); a history of neurological disease; or were experiencing significant akathisia (global score of >2 on the Barnes Akathisia Rating Scale) (Barnes, 1989) or extrapyramidal symptoms (>2 on >2 items of the Simpson Angus Scale) (Simpson et al., 1970).

HC participants were excluded if they met diagnostic criteria for any Axis I disorder; or had a family history of a psychotic disorder in a first-degree relative. Participants were recruited through outpatient clinics and research registries at the Centre for Addiction and Mental Health (CAMH), as well as through online advertising. The local research ethics board approved this study, and all participants provided written informed consent.

3.3.2 Measures

To evaluate consummatory and anticipatory pleasure, all participants completed the self-report Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006). The TEPS is comprised of 18 items depicting in-the-moment or anticipated pleasurable experiences, for which participants rate their agreement on a 6-point Likert scale, providing scores for the consummatory (TEPS-Con) and anticipatory subscales (TEPS-Ant) of the TEPS. The TEPS has demonstrated high internal consistency across studies evaluating the experience of pleasure in patients with schizophrenia (Gard et al., 2006, Strauss et al., 2011). In addition,
participants were administered the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982), and the Apathy Evaluation Scale - Clinician Version (AES-C; Marin et al., 1991), to evaluate the severity of positive symptoms, negative symptoms, and motivation deficits, respectively. The SANS total score was calculated based on the sum of the items in the Affective Flattening, Avolition-Apathy, and Anhedonia-Asociality subscales, as well as the Poverty of Speech item (excluding Inappropriate Affect, Poverty of Content of Speech, Blocking, and the Attention subscale and all global items) (Foussias and Remington, 2010). Neurocognition was also assessed in all participants using the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004). Lastly, in a subsample of 108 participants, the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1990) was also administered to assess for depressive symptoms.

3.3.3 Analyses

Group differences in demographic and clinical variables were assessed using chi-square tests and t-tests, as appropriate. A MANOVA with TEPS-Con and TEPS-Ant as dependent variables, and diagnostic group (i.e. HC vs. SZ) as the independent variable was conducted to assess for group differences in consummatory and anticipatory pleasure. In order to explore the impact of amotivation severity on TEPS-Con and TEPS-Ant specifically in SZ, this group was categorized according to level of amotivation severity through a tertile split of AES scores. A second MANOVA, with TEPS-Con and TEPS-Ant as the dependent variables and amotivation group (HCs vs. low vs. moderate vs. high amotivation SZ) as the independent variable was then conducted to evaluate differences in TEPS-Con and TEPS-
Ant between healthy controls and schizophrenia patients across low, moderate, and high levels of amotivation.

Examination of the influence of amotivation and diagnostic group (i.e. HC vs. SZ) on TEPS-Con and TEPS-Ant was conducted through a series of hierarchical multiple regressions. First, to determine the model of best fit, exploratory regression analyses were conducted with both linear and quadratic AES terms as predictors. Based on these results, subsequent hierarchical regressions were then conducted to determine the independent predictive value of both amotivation and diagnostic group on TEPS-Con and TEPS-Ant.

In addition, Pearson correlations were calculated to determine the relationship between TEPS-Con, TEPS-Ant and clinical measures. Cronbach’s alpha was also calculated as a measure of internal consistency within each TEPS subscale, as well as the total scale. SZ participants’ antipsychotic medication dosages were converted into chlorpromazine (CPZ) equivalents (Gardner et al., 2010; Leucht et al., 2016). All analyses were conducted with the Statistical Package of Social Science (SPSS) version 24.

3.4 Results

3.4.1 Participant demographics and clinical characteristics

The demographic and clinical characteristics of the sample are displayed in Table 3-1. Groups were well matched for age and sex; however SZ participants had significantly fewer years of education compared to HCs ($t(152)=3.862, p<0.001$). Approximately 90% of SZ participants were treated with a single atypical antipsychotic (i.e. monotherapy). SZ
participants had a wide range of illness duration (1 to 39 years), with a mean duration of illness of 11.8 years.

Table 3-1: Sample demographics and clinical characteristics of HC and SZ participants.

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls (HC) n=81</th>
<th>Schizophrenia (SZ) n=84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.3 (11.3)</td>
<td>35.0 (10.4)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>45:36</td>
<td>49:35</td>
</tr>
<tr>
<td>Education</td>
<td>15.4 (2.6)</td>
<td>13.9 (2.4)***</td>
</tr>
<tr>
<td>Years of Illness</td>
<td>-</td>
<td>11.8 (8.7)</td>
</tr>
<tr>
<td>Medication</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CPZ Equivalents</td>
<td>531.2 (292.6)</td>
<td></td>
</tr>
<tr>
<td>Typical Antipsychotics</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Atypical Antipsychotics</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Diagnosis (SZ:SA)</td>
<td>-</td>
<td>69:15</td>
</tr>
<tr>
<td>SAPS Total</td>
<td>-</td>
<td>17.3 (14.6)</td>
</tr>
<tr>
<td>SANS Total</td>
<td>3.1 (5.2)</td>
<td>18.8 (12.1)***</td>
</tr>
<tr>
<td>AES-C</td>
<td>28.1 (5.3)</td>
<td>37.2 (7.4)***</td>
</tr>
<tr>
<td>CDSS</td>
<td>0.7 (1.2)</td>
<td>2.4 (2.5)***</td>
</tr>
<tr>
<td>BACS</td>
<td>0.2 (1.1)</td>
<td>-1.5 (1.2)***</td>
</tr>
</tbody>
</table>

Note: Data are presented as means and standard deviations. Group differences are significant at \( p<0.05^*, p<0.01^{**}, p<0.001^{***} \).

(Abbreviations: SZ: Schizophrenia; SA: Schizoaffective Disorder; SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; AES-C: Apathy Evaluation Scale – Clinician Version; CDSS: Calgary Depression Scale for Schizophrenia, BACS: Brief Assessment of Cognition in Schizophrenia)
Demographic and clinical characteristics of patients across amotivation severity groups are displayed in Table 3-2. Low, moderate and high amotivated SZ patients did not differ in age, years of illness, or depression but did differ in antipsychotic dosage \((F(2,83)=3.673, p=0.030)\), cognitive functioning \((F(2,83)=3.236, p=0.044)\), positive symptoms \((F(2,83)=11.078, p<0.001)\) and negative symptoms \((F(2,83)=31.409, p<0.001)\).
Table 3-2: Demographic and clinical characterization of SZ patients across levels of amotivation severity.

<table>
<thead>
<tr>
<th></th>
<th>Low Amotivation SZ n=29</th>
<th>Moderate Amotivation SZ n=31</th>
<th>High Amotivation SZ n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.3 (9.7)</td>
<td>37.2 (11.2)</td>
<td>32.9 (10.0)</td>
</tr>
<tr>
<td>Years of Illness</td>
<td>11.3 (7.0)</td>
<td>13.8 (10.6)</td>
<td>9.7 (7.5)</td>
</tr>
<tr>
<td>CPZ*</td>
<td>427.0 (239.6)</td>
<td>625.5 (313.6)</td>
<td>535.3 (291.7)</td>
</tr>
<tr>
<td>SAPS Total*** c</td>
<td>8.9 (8.4)</td>
<td>18.5 (15.0)</td>
<td>25.8 (15.0)</td>
</tr>
<tr>
<td>SANS Total*** c</td>
<td>9.4 (5.1)</td>
<td>19.4 (10.2)</td>
<td>29.4 (11.4)</td>
</tr>
<tr>
<td>AES*** c</td>
<td>29.6 (3.4)</td>
<td>37.5 (2.2)</td>
<td>46.0 (4.6)</td>
</tr>
<tr>
<td>CDSS</td>
<td>1.9 (2.5)</td>
<td>2.8 (2.7)</td>
<td>2.8 (1.8)</td>
</tr>
<tr>
<td>BACS* b</td>
<td>-1.1 (1.1)</td>
<td>-1.6 (1.1)</td>
<td>-1.9 (1.2)</td>
</tr>
</tbody>
</table>

See Table 3-1 for abbreviations. Group differences are significant at $p<0.05^*$, $p<0.01^{**}$, or $p<0.001^{***}$. In addition, $^a$ denotes significant pairwise differences where High=Low>Moderate, $^b$ denotes High=Moderate <Low, $^c$ denotes High>Moderate>Low.
3.4.2 Consistency of self-report on the TEPS

Cronbach’s alpha for the TEPS total scale (SZ: $\alpha=0.87$; HC: $\alpha=0.79$), TEPS-Con (SZ: $\alpha=0.74$; HC: $\alpha=0.68$) and TEPS-Ant (SZ: $\alpha=0.80$; HC: $\alpha=0.72$) subscales revealed adequate reliability, suggestive of consistent responding in both groups.

3.4.3 Group differences in consummatory and anticipatory pleasure

The first MANOVA revealed no significant main effect of diagnosis ($F(2,162)=1.889$, $p=0.155$, $\eta^2=0.023$) on either TEPS-Con or TEPS-Ant. The second MANOVA revealed a significant amotivation group effect ($F(6,322)=3.094$, $p=0.006$, $\eta^2=0.055$) for both TEPS-Con ($F(3,161)=5.341$, $p=0.002$) and TEPS-Ant ($F(3,161)=4.933$, $p=0.003$) (Figure 3-1). Post-hoc comparisons revealed significant differences in both TEPS-Con and TEPS-Ant between the high and low amotivation SZ groups (TEPS-Con: $p<0.001$; TEPS-Ant: $p=0.001$); between the high and moderate amotivation SZ groups (TEPS-Con: $p=0.041$; TEPS-Ant: $p=0.026$) and between the high amotivation SZ group and HCs (TEPS-Con: $p<0.001$; TEPS-Ant: $p<0.001$), such that TEPS-Con and TEPS-Ant were lower in the high amotivation SZ group. There were no significant differences between the HC group, the low amotivation SZ group, and the moderate amotivation SZ group. After Bonferroni correction for multiple comparisons, differences between the high and moderate amotivation SZ groups were no longer significant, while other pairwise differences remained unchanged. Controlling for the effects of cognitive functioning did not significantly change the results. Further, covarying for level of positive symptoms across the low, moderate and high amotivation SZ groups did not significantly change the results.
Figure 3-1: Mean consummatory (TEPS-Con) and anticipatory (TEPS-Ant) pleasure ratings for HCs and SZ patients across amotivation severity levels. Group differences are significant at $p<0.05^*$, or $p<0.01^{**}$. 
3.4.4 Relationships between amotivation, diagnostic group, and consummatory and anticipatory pleasure

The results of the first set of hierarchical multiple regressions revealed that a linear model provided the best fit for the relationship between consummatory pleasure and amotivation ($F(1,163)=19.811, p<0.001, R^2=0.108$) (Figure 3-2). For anticipatory pleasure, however, a quadratic model was found to best fit the relationship with amotivation ($F(2,162)=10.526, p<0.001, R^2=0.115$), with the addition of the quadratic term significantly increasing model fit compared to a linear model ($F(1,162)=5.995, p=0.015, \text{increase in } R^2=0.033$), primarily driven by the SZ group ($F(2,81)=7.492, p=0.001, R^2=0.156$). Accordingly, we utilized a quadratic model (i.e. AES and AES squared term) in subsequent regression analyses for TEPS-Ant.
Figure 3-2: Scatterplots and regression lines for the significant relationships between amotivation (AES) and A) consummatory pleasure (TEPS-Con) and B) anticipatory pleasure (TEPS-Ant) across the entire sample. Regression lines represent a linear model for A) TEPS-Con (y=−0.0341x + 5.6219) and a quadratic model for B) TEPS-Ant (y=−0.0017x^2 + 0.0915x + 3.4047).
The second set of hierarchical regressions examining the contributions of amotivation and diagnostic group to the prediction of pleasure ratings revealed that amotivation is a significant predictor of both consummatory \( F(1,163)=19.811, p<0.001, R^2=0.108 \) and anticipatory pleasure \( F(2,162)=10.526, p<0.001, R^2=0.115 \), with no independent contribution from diagnostic group.

### 3.4.5 Clinical correlates of consummatory and anticipatory pleasure

Across the entire sample, both TEPS-Con and TEPS-Ant were correlated with the AES (TEPS-Con: \( r=-0.33, p<0.001 \); TEPS-Ant: \( r=-0.29, p<0.001 \)) and SANS total scores (TEPS-Con: \( r=-0.23, p=0.003 \); TEPS-Ant: \( r=-0.29, p<0.001 \)). Neither TEPS-Con nor TEPS-Ant was correlated with age, education, positive symptoms or depression. Within the SZ group, our results revealed that TEPS-Con and TEPS-Ant were significantly correlated with AES and SANS scores (Table 3-3). TEPS-Con and TEPS-Ant were not correlated with age, education, duration of illness or antipsychotic dosage.
Table 3-3: Correlations between consummatory and anticipatory pleasure, and clinical and cognitive measures in participants with schizophrenia.

<table>
<thead>
<tr>
<th></th>
<th>TEPS-Con</th>
<th>TEPS-Ant</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS Total</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>SANS Total</td>
<td>-0.25*</td>
<td>-0.35**</td>
</tr>
<tr>
<td>AES</td>
<td>-0.40***</td>
<td>-0.32**</td>
</tr>
<tr>
<td>CDSS</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>BACS</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

See Table 3-1 for abbreviations. Correlations are significant at \( p<0.05 \), \( p<0.01 \), \( p<0.001 \); ns: not significant (\( p>0.1 \)).
3.5 Discussion

Anhedonia has long been considered a core symptom of schizophrenia, but the nature of this deficit is not well understood. Accordingly, this study sought to evaluate consummatory and anticipatory pleasure as measured by the TEPS across schizophrenia and healthy control participants.

3.5.1 Diagnosis

One of the prevailing difficulties in understanding the emotion paradox in schizophrenia is the inconsistent results across studies using the TEPS. In this study, we did not find a main effect of diagnosis for either consummatory or anticipatory pleasure. Though our finding of intact consummatory pleasure between schizophrenia and healthy participants is consistent with the current literature, our null finding of anticipatory pleasure between groups is somewhat unexpected (Cassidy et al., 2012; Edwards et al., 2015; Favrod et al., 2009; Gard et al., 2006; Loas et al., 2009). However, the findings of the present study are in line with two experimental studies using objective computerized tasks to evaluate consummatory and anticipatory pleasure, such that schizophrenia patients were shown to exhibit similar levels of in-the-moment and anticipated pleasure compared to healthy controls (Choi et al., 2014; Trémeau et al., 2010).

While we did not find a difference in anticipatory pleasure as a function of diagnosis, it is important to note that mean TEPS-Ant scores in our sample were similar to those reported by other studies (Edwards et al., 2015; Gard et al., 2007; Strauss et al., 2011), but notably higher than that found by Gard et al. (2007) for schizophrenia patients. Closer examination of sample differences across studies, in an effort to ascertain the contributors to
the lower anticipatory pleasure in Gard et al. (2007) suggest a potential role of antipsychotic
class. Specifically, there are notable differences in the proportion of patients treated with
typical versus atypical antipsychotics, with 9% of schizophrenia patients treated with typical
antipsychotics in our study, 12% in Strauss et al. (2011), and 31% in Gard et al. (2007). This
pattern has also been observed in other studies that have failed to find differences in
anticipatory pleasure (Cassidy et al., 2012; Edwards et al., 2015). Further, neuroimaging and
behavioural findings have suggested reward system dysfunctions in patients treated with
typical antipsychotics (Juckel et al., 2006b; Schlagenhauf et al., 2008). This raises the
possibility that differences in the TEPS may be subject to the same process.

3.5.2 Amotivation

In light of earlier work by Chan et al, (2010) suggesting differential ratings on
pleasure as a function of negative symptoms, we also examined the relationship between the
experience of pleasure and amotivation. We opted to investigate amotivation specifically,
because of work suggesting that motivational deficits represent the most central feature of
negative symptoms (Foussias and Remington, 2010). Further, consummatory and
anticipatory pleasure capture the hedonic components of the larger motivational framework
which serve to inform goal-directed behaviour. Our results revealed that amotivation
significantly predicted both consummatory and anticipatory pleasure across the entire
sample. Moreover, diagnostic group did not significantly contribute any independent
predictive value above and beyond the effects of amotivation, further supporting our
aforementioned absence of an effect of diagnostic group.
Though it is important to acknowledge that difficulties with motivation – or gradients of them – are ubiquitous, the distribution of amotivation severity is different for patients and healthy individuals. As expected, there is a broader range of motivation deficits in patients with schizophrenia compared to healthy controls, hindering comparisons between the two participant groups at the extremes. Thus, we extended our dimensional examination of consummatory and anticipatory pleasure across levels of amotivation severity in patients with schizophrenia only. Our results revealed a significant main effect of amotivation group, such that schizophrenia patients with high levels of amotivation were significantly impaired in consummatory and anticipatory pleasure compared to those at both low and moderate levels, and compared to healthy controls. These results suggest that deficits in the experience of pleasure are primarily driven by patients with the highest severity of amotivation. This finding fits well with the quadratic model explaining the curvilinear relationship between anticipatory pleasure and amotivation, such that low and moderately amotivated schizophrenia patients cluster around the peak of the curve, with a dramatic decline towards the more severe end of the amotivation spectrum. Moreover, these results are also in line with the framework proposed by Strauss and Gold (2012), with reduced pleasure-seeking behaviour – likely subserved by deficits in motivation – representing a facet of anhedonia in schizophrenia. Taken together, these results provide further evidence for the suggested link between impairments in discrete aspects of pleasure and broader motivation deficits (Raffard et al., 2013). These findings may also shed further light on potential underlying causes for the discrepant findings across previous studies using the TEPS, with categorical differences across diagnostic groups potentially driven by different distributions of motivation deficits between schizophrenia samples in these studies.
It is also interesting that schizophrenia patients with moderate levels of amotivation reported similar levels of consummatory and anticipatory pleasure compared to both the low amotivation schizophrenia group, and healthy controls. Though the finding of comparable levels of consummatory and anticipatory pleasure between healthy controls and patients with low amotivation is not entirely surprising, the findings for moderately amotivated patients are somewhat unexpected. It is possible that a hedonic impairment does indeed exist for the moderate group, but with a small effect size that would require a larger sample to detect. However, another possible explanation for these results is that moderately amotivated patients experience oscillations between intact and impaired motivation states, rather than stable moderate impairment. During these periods of intact motivation, patients experience both interest in, and enjoyment from goal-directed activities. The discrepancy between these extremes may be poignant enough to lead one to believe that things can get better. Thus, the sense of hope and optimism gained from these periods of intact motivation – though temporary – may enable the persistence of current and expected future pleasure (Cummins and Nistico, 2002). Though speculative, this potential mechanism warrants further investigation.

3.5.3 Limitations

There are some limitations to this study that should also be noted. Firstly, groups were not matched by education. Given the underlying cognitive component of emotional self-report measures such as the TEPS, level of education may influence ratings, though it is important to note that education was not correlated with either consummatory or anticipatory pleasure. Further, all patients were being treated with antipsychotic medications, and while the extent of dopamine antagonism may influence the experience of pleasure along a
continuum, recent work has suggested this may not in fact be the case (Fervaha et al., 2016a). We took additional steps to minimize the potential effects of antipsychotic treatment and other sources of secondary negative symptoms in this study, through exclusion of schizophrenia participants with clinically significant extrapyramidal symptoms. In addition, the distribution of our sample with regards to treatment with atypical versus typical antipsychotics, although consistent with most recent studies in this population, did not permit a formal investigation of the effects of antipsychotic class on the experience of pleasure.

3.5.4 Conclusions

In summary, the current findings suggest that deficits in consummatory and anticipatory pleasure are strongly linked to higher levels of amotivation, rather than merely as a result of having a diagnosis of schizophrenia. Further exploration in patients with schizophrenia suggests that hedonic deficits are driven specifically by those individuals at the most severe end of the spectrum. Although we failed to replicate the main findings of the original study by Gard et al., (2007) of a specific impairment in anticipatory pleasure in schizophrenia, our results highlight the importance of investigating hedonic deficits as they relate to a spectrum of amotivation, in addition to diagnostic status. Moving forward, future studies utilizing enriched samples with a wide range of motivation deficits may offer further clarification around the factors and processes that contribute to differences in the experience of pleasure across subpopulations of individuals with schizophrenia. Moreover, replication of these results is required to confirm the proposed quadratic relationship between anticipatory pleasure and amotivation. Lastly, the incorporation of objective and experiential paradigms in this future work may help clarify the relationship between self-reported and experienced in-the-moment pleasure as a function of both amotivation and a diagnosis of schizophrenia.
Chapter 4

Chapter 4: An examination of the multi-faceted motivation system in healthy young adults: the impact of schizotypal, depressive and amotivation symptoms

4.1 Abstract

Background: Amotivation is a significant predictor of poor functional outcomes in individuals with schizophrenia and depression. Inconsistent findings regarding the precise reward deficits in these disorders have been attributed to confounding variables such as medication effects, as well as cognitive impairment. Thus, investigating the motivational framework in a non-clinical sample may further our understanding of the specific processes underlying these deficits, while minimizing the effects of illness-specific confounds.

Methods: One hundred seventeen healthy undergraduate students were evaluated for amotivation, schizotypal traits, depressive symptoms, and cognition, followed by objective computerized tasks to measure the different facets of motivation. Hierarchical regressions were conducted to determine the predictive contributions of schizotypy, depression, cognition, and amotivation on task performance.

Outcomes: Amotivation was a significant predictor of objective in-the-moment experience of pleasure, as well as subjective reports of both consummatory and anticipatory pleasure in a non-clinical sample, with little to no independent contribution from schizotypal and depressive symptoms. Further, correlational analyses revealed that both reward and effort
valuation may serve to guide effort-cost computations.

Interpretations: We found that in a healthy undergraduate sample, amotivation predicts reward processing impairments. Further, motivation deficits are related to a reduction in reward responsiveness. It remains to be seen whether relationships between amotivation and reward processing are similar or different in clinical populations with more severe impairment.
4.2 Introduction

Amotivation, a reduction in the ability to initiate and/or sustain goal-directed behaviour, is a prevalent symptom in both schizophrenia and major depressive disorder, and is inextricably linked to poor functional outcomes in these individuals (Fervaha et al., 2016, 2015; Foussias et al., 2009; Wells et al., 1989). Motivation has been conceptualized as a multi-faceted construct comprised of: 1) hedonic experience (i.e., reward responsiveness or “liking”); 2) reward expectancy (i.e., “wanting”); 3) reward valuation; 4) effort valuation; and 5) goal-directed decision-making (Barch and Dowd, 2010). Accordingly, impairments in any one of these facets can contribute to the manifestation of clinical amotivation. With schizotypal and depressive traits in non-clinical populations positioned on continua that extend to their respective clinical populations (Kendler and Gardner, 1998; Linscott and van Os, 2013; van Os et al., 2000), investigation of the multi-faceted motivation system in non-clinical samples may afford insights into specific processes that contribute to clinical amotivation seen in schizophrenia and depression, while minimizing illness-specific confounds. To our knowledge, no study to date has concurrently examined the multiple facets that comprise the motivation system in a population of healthy young adults.

To date, most studies examining illness-related motivation deficits have utilized separate clinical samples of individuals with schizophrenia or depression. Evidence from imaging and behavioural studies suggests that patients with schizophrenia have impaired reward valuation, reward expectancy, effort valuation, and goal-directed decision making, but intact hedonic capacity (Barch et al., 2016; Barch and Dowd, 2010; Kring and Barch, 2014). In contrast, patients with depression are impaired in reward responsiveness, effort
valuation, and goal-directed decision-making (Barch et al., 2016; Treadway and Zald, 2011). However, these findings have been inconsistent across studies (Barch et al., 2016), with discrepancies attributed to differences in cognitive functioning (i.e. memory, recall), antipsychotic class (i.e. typical vs. atypical) and symptom severity (i.e. anhedonia, negative symptoms, amotivation) across clinical samples (Beninger et al., 2003; Cassidy et al., 2012; Gold et al., 2015; Schlagenhauf et al., 2008; Strauss and Gold, 2014). Studies examining these constructs in non-clinical samples have been limited, with the majority of the existing literature focusing on isolated facets – particularly anhedonia – in separate subclinical depressive or schizotypal samples (Chan et al., 2012; Liu et al., 2011; McCarthy et al., 2015; Yan et al., 2011).

The present study sought to examine the impact of amotivation, schizotypal, and subsyndromal depressive symptoms on specific motivation system constructs in a non-clinical sample using objective computerized psychometric tasks. We hypothesized that poorer performance across tasks would be correlated with more severe amotivation. Further, we hypothesized that higher schizotypal traits would be linked to deficits in reward expectancy and effort valuation, with more severe depressive symptoms related to impairments in reward responsiveness and reward valuation.
4.3 Materials & Methods

4.3.1 Participants

Participants in this study consisted of 117 undergraduate students at the University of Toronto Scarborough, who were recruited through an online experiment registry for students in undergraduate psychology courses, and voluntarily participated for course credit. Participants were between the ages of 17-38, fluent in English, and capable of providing informed consent. Participants were excluded if they were taking any psychotropic medications, diagnosed with a current or past schizophrenia-spectrum illness, had a history of substance abuse or dependence within the past six months, a history of neurological disease, or a history of head trauma with loss of consciousness for more than 30 minutes. The local research ethics board approved this study, and all participants provided written informed consent.

4.3.2 Measures

4.3.2.1 Self-report Measures

Participants completed a battery of self-report measures of amotivation, hedonic capacity, schizotypy, and depressive symptoms. Specifically, amotivation was assessed using the self-report version of the Apathy Evaluation Scale (AES-S; Marin et al., 1991). The Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006), an 18-item self-report questionnaire evaluated consummatory (TEPS-Con) and anticipatory (TEPS-Ant) pleasure. The Likert-scale version of the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) was administered to assess for schizotypal traits, from which positive (SPQ-Pos), negative
(SPQ-Neg) and disorganized (SPQ-Dis) schizotypy subscores were also calculated. Depressive symptoms were assessed using the Centre for Epidemiologic Studies – Depression Scale (CES-D; Radloff, 1977). In addition, global cognitive functioning was assessed using the Brief Neurocognitive Assessment, consisting of tests of working memory and processing speed (Fervaha et al., 2014). Lastly, the Dot Counting Test (DCT) was administered to assess for performance validity (Boone et al., 2002).

4.3.2.2 Objective Computerized Measures

A series of objective computerized psychometric tasks were subsequently administered to measure each facet of the motivation system. Task administration was randomized to minimize order effects.

Reward Responsiveness

The International Affective Picture System (IAPS) was used to assess for reward responsiveness or “liking”, with in-the-moment ratings of pleasantness (IAPS-Pleasant) and arousal (IAPS-Arousal) on a 9-point Likert scale (Heerey and Gold, 2007). Given our interest in reward-driven processes we focused our analyses on positive-valence images only, with higher ratings reflecting greater capacity to experience pleasure in response to positive stimuli.
**Reward Expectancy**

The Cued Reinforcement Reaction Time (CRRT) task was used to assess for reward expectancy or “wanting” (Cools et al., 2005). Briefly, the CRRT requires rapid “odd-one-out” judgments involving differentially reinforced cues, such that participants are rewarded most points when responding fast to high probability reinforcement trials. The variable of interest is the degree of anticipated reinforcement-related speeding (CRRT-RRS), calculated by subtracting the median reaction time (RT) for low probability trials from the median RT for the high probability trials (smaller values indicating greater RRS).

**Reward Valuation**

Reward valuation was assessed using the Kirby Delay Discounting (Kirby DD) task, where respondents choose between a small immediate reward or a larger reward delayed over a varying number of days, and thus measures participants’ differential valuation of monetary rewards over time (Kirby and Maraković, 1996). The outcome of interest is the rate at which participants discount the value of future rewards, calculated as the natural logarithm (ln) of the discounting rate ($k$) when the delayed reward is small (Kirby-Small), medium (Kirby-Med), or large (Kirby-Large). Smaller values are indicative of lower discounting rates, or less impulsivity.

**Effort Valuation**

Effort valuation was assessed using the Effort Expenditure for Rewards Task (EEfRT), which measures participants’ willingness to expend effort for monetary gains (Treadway et al., 2009). Here, participants choose between two effortful tasks according to
difficulty (easy vs. hard), across trials with differing reward magnitudes (i.e. ranging from $1.00-$4.85) and reward likelihood (i.e. 12%, 50%, 88%). Easy and hard tasks differed in effort requirement as determined by number of button presses (i.e. 30 vs. 100). The variables of interest are total number of hard tasks chosen (EEfRT-Total) and EEfRT-Net, which is calculated as the number of hard tasks chosen at the high probability level minus the number of hard tasks chosen at the low probability condition.

**Goal-Directed Decision-Making**

Lastly, goal-directed decision-making was assessed using the Multitasking in the City Test (MCT; Jovanovski et al., 2012), a virtual reality task in which participants are asked to use a joystick to navigate and complete a number of errands in a virtual city (e.g. buy groceries, attend a doctor’s appointment, etc.). The outcome variables are the total distance travelled (MCT-Distance; in virtual environment units - VEUs) and performance score (MCT-Performance), calculated as the total number of tasks completed minus total omission and commission errors (i.e. tasks failed or repeated, respectively). Shorter distances and higher performance scores indicate better decision-making.

All self-report scales and objective motivation tasks, except for the Multitasking in the City Task (MCT), were programmed and administered on Open Sesame v. 2.9.4 (Mathôt et al., 2012).
4.4. Analyses

4.4.1 Effort validity

The DCT was used to assess for performance validity. Participants with a score greater than or equal to 14 (n=12), a well-validated cut-off score for a healthy undergraduate sample (An et al., 2012; Boone et al., 2002), as well as those with missing DCT scores (n=16) were deemed invalid. The analyses were first conducted including all participants in an effort to conserve statistical power (results shown). To ensure validity, however, these analyses were repeated after excluding participants who exerted non-credible test findings (not reported unless different from results of entire sample).

4.4.2 Statistical Analyses

Primary analyses consisted of hierarchical multivariate regressions to assess for the predictive value of illness-related symptoms on the multiple facets of motivation. In the first regression, CES-D and SPQ total scores were entered into the first step, followed by AES in the second step. A second regression model was repeated with BNA scores entered as an additional variable in the first step to evaluate possible confounding effects of cognition, followed by AES in the second step. To further explore bivariate relationships between motivation tasks and clinical measures, Spearman correlations were conducted due to non-normal variable distributions. The false discovery rate (FDR) correction was utilized to account for multiple comparisons, with q values less than 0.05 considered statistically significant (Storey and Tibshirani, 2003). In addition, Cronbach’s alpha was calculated for each self-report measure to ensure consistent responding across the sample. All analyses were conducted with the Statistical Package of Social Science (SPSS) version 24.
4.5 Results

4.5.1 Demographics and clinical characterization

Sample demographics and symptom characteristics are shown in Table 4-1. Participants in this sample had a mean age of 19.9 years, with an average of 13.5 years of education.
Table 4-1: Sample demographics and symptom characterization.

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>45:72</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>19.9 (2.9)</td>
<td>17.0-38.0</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>13.5 (1.4)</td>
<td>11.0-18.0</td>
</tr>
<tr>
<td>TEPS-Con</td>
<td>4.6 (0.8)</td>
<td>2.5-6.0</td>
</tr>
<tr>
<td>TEPS-Ant</td>
<td>4.6 (0.7)</td>
<td>2.3-5.9</td>
</tr>
<tr>
<td>AES-S</td>
<td>30.4 (5.7)</td>
<td>20.0-49.0</td>
</tr>
<tr>
<td>CES-D</td>
<td>16.3 (10.3)</td>
<td>0.0-48.0</td>
</tr>
<tr>
<td>SPQ Total</td>
<td>117.8 (34.5)</td>
<td>14.0-207.0</td>
</tr>
<tr>
<td>SPQ Positive</td>
<td>48.0 (18.2)</td>
<td>0.0-99.0</td>
</tr>
<tr>
<td>SPQ Negative</td>
<td>42.9 (16.5)</td>
<td>1.0-81.0</td>
</tr>
<tr>
<td>SPQ Disorganization</td>
<td>26.9 (11.3)</td>
<td>0.0-52.0</td>
</tr>
<tr>
<td>BNA Global</td>
<td>-.19 (0.8)</td>
<td>-2.1-2.1</td>
</tr>
</tbody>
</table>

(Abbreviations: TEPS-Con: Temporal Experience of Pleasure-Consummatory subscale; TEPS-Ant: Temporal Experience of Pleasure-Anticipatory subscale; AES-S: Apathy Evaluation Scale –Self-report version; CES-D: Centre for Epidemiologic Studies- Depression Scale; SPQ: Schizotypal Personality Questionnaire; BNA: Brief Neurocognitive Assessment).
4.5.2 Consistency of self-report clinical measures

Cronbach’s alpha for the TEPS (TEPS-Con: $\alpha=.63$; TEPS-Ant: $\alpha=.73$), AES ($\alpha=.78$), CES-D ($\alpha=.90$) and SPQ (SPQ-Pos: $\alpha=.92$; SPQ-Neg: $\alpha=.91$; SPQ-Dis: $\alpha=.91$) revealed adequate reliability across all scales, suggestive of consistent responding amongst participants.

4.5.3 Hierarchical Regressions

The first hierarchical multivariate regression revealed a significant main effect of CES-D ($F(9,90)=2.081, p=.039$), specifically in predicting TEPS-Ant ($\beta=-.025, p<.001$), as well as IAPS pleasantness ratings ($\beta=-.020, p=.050$) and a trend for TEPS-Con ($\beta=-.014, p=.059$), with no independent contribution from SPQ scores ($p=.17$) in the first step, though this main effect of CES-D did not remain significant after excluding invalid responders (CES-D: $p=.10$). The addition of amotivation in the second step was significant ($F(9,89)=2.746, p=.007$), with AES as a significant predictor of IAPS pleasantness ratings ($\beta=-.059, p=.001$), TEPS-Con ($\beta=-.035, p=.015$), and TEPS-Ant ($\beta=-.051, p<.001$).

Moreover, after including AES in the model, the effect of CES-D was no longer significant ($p=.31$). The second hierarchical regression revealed no significant predictive value of depression, schizotypy or cognition in the first step. However, the addition of AES into the second step revealed that both amotivation ($F(9,71)=3.103, p=.003$) and cognition ($F(9,71)=2.053, p=.046$) independently predicted overall motivation task performance, though the effect of cognition was not significant after excluding invalid responders ($p=.16$). In the final model, amotivation significantly predicted IAPS pleasantness ratings ($\beta=-.067, p=.001$), TEPS-Con ($\beta=-.052, p=.003$) and TEPS-Ant ($\beta=-.062, p<.001$).
4.5.4 Correlational analyses

Bivariate correlations between clinical measures and motivation task performance are shown in Table 4-2. Interestingly, the AES was only correlated with IAPS ratings for pleasantness and arousal. Further, IAPS pleasantness ratings were correlated with both TEPS-Con and TEPS-Ant, whereas IAPS arousal ratings were only correlated with TEPS-Ant. Negative schizotypal traits were negatively correlated with IAPS pleasantness and arousal ratings, but positively correlated with CRRT and EEfRT task performance. Lastly, cognitive functioning was correlated with the EEfRT task.
Table 4-2: Bivariate correlations between clinical measures and motivation tasks.

<table>
<thead>
<tr>
<th></th>
<th>AES</th>
<th>CES</th>
<th>SPQ-Total</th>
<th>SPQ-Pos</th>
<th>SPQ-Neg</th>
<th>SPQ-Dis</th>
<th>TEP Con</th>
<th>TEP Ant</th>
<th>BNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAPS-Pleasant</td>
<td>-.33**a</td>
<td>-.20*</td>
<td>-</td>
<td>-</td>
<td>-.29**a</td>
<td>-</td>
<td>.34**a</td>
<td>.42**a</td>
<td>-</td>
</tr>
<tr>
<td>IAPS-Arousal</td>
<td>-.24**</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-.35**a</td>
<td>-</td>
<td>-</td>
<td>.30**a</td>
<td>-</td>
</tr>
<tr>
<td>CRRT-RRS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Kirby-Small</td>
<td>-</td>
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<tr>
<td>Kirby-Med</td>
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<tr>
<td>Kirby-Large</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EEfRT-Total</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EEfRT-Net</td>
<td>.21*</td>
<td>.20*</td>
<td>.32**a</td>
<td>.23*</td>
<td>.27**</td>
<td>.23*</td>
<td>-</td>
<td>-</td>
<td>.22*</td>
</tr>
<tr>
<td>MCT-Distance</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-.19*</td>
<td>-</td>
<td>-</td>
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<tr>
<td>MCT-Performance</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Note: Correlations are significant at $p < 0.05^*$, or $p < 0.01^{**}$; "a" denotes $q < 0.05$.

(See table 4-1 for abbreviations; in addition, IAPS: International Affective Picture System; CRRT-RRS: Cued-Reinforcement Reaction Time Task-Reinforcement Related Speeding; EEfRT: Effort Expenditure for Rewards Task; MCT: Multitasking in the City Test).
4.5.5 Inter-task correlations

Correlations were also conducted to examine interrelationships between motivation task variables. As shown in Table 4-3, Kirby rates, specifically for small delayed rewards, were negatively correlated with total number of hard choices on the EEfRT.

Table 4-3: Inter-task correlations.

<table>
<thead>
<tr>
<th></th>
<th>2</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IAPS- Pleasant</td>
<td>.44**a</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>2. IAPS- Arousal</td>
<td></td>
<td>-</td>
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<tr>
<td>3. CRRT-RRS</td>
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<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4. Kirby-Small</td>
<td></td>
<td></td>
<td></td>
<td>.85**a</td>
<td>.79**a</td>
<td>-.23*</td>
<td>-.21*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5. Kirby-Med</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.85**a</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6. Kirby-Large</td>
<td></td>
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<td>-</td>
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<td>7. EEfRT- Total</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>.37**a</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8. EEfRT-Net</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>-</td>
<td>.30**a</td>
</tr>
<tr>
<td>9. MCT- Distance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-.46**a</td>
</tr>
<tr>
<td>10. MCT- Performance</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Note: Correlations are significant at $p < 0.05^*$, or $p < 0.01^{**}$; $^a$ denotes $q < 0.05$. See table 4-2 for abbreviations.
4.6 Discussion

The present study aimed to ascertain the impact of subclinical levels of schizotypy and depression, amotivation and cognitive functioning on the multiple facets of the motivation system. Our regression models revealed that only amotivation emerged as a significant predictor of objective performance across motivation system tasks. Schizotypal traits, depressive symptoms, and cognitive performance, particularly after excluding non-credible participants, did not offer any additional predictive value. Further, amotivation appeared to specifically predict pleasantness and arousal ratings on the IAPS, as well as self-reported consummatory and anticipatory pleasure on the TEPS. These results are congruent with studies suggesting a relationship between anhedonia and amotivation (Raffard et al., 2013). Indeed, recent work by our own group demonstrated that hedonic deficits are primarily driven by higher severity of amotivation across a sample of healthy controls and schizophrenia patients, irrespective of diagnosis (Da Silva et al., 2017). The present results extend this relationship of amotivation with both current and non-current pleasure in a non-clinical sample. Taken together, our findings suggest that reduced reward responsiveness may be the driving force underlying amotivation in a healthy undergraduate sample. That is, if an individual cannot enjoy a pleasurable experience in the moment, they will be less likely to pursue it, thus contributing to motivational deficits.

Drawing from the schizophrenia and depression literature where motivation deficits have been repeatedly linked to impairments across a number of reward-system processes, we also hypothesized that higher levels of amotivation would be related to poorer performance on reward expectancy, reward valuation, effort valuation, and goal-directed decision-making
tasks. Contrary to our hypotheses, however, amotivation did not predict performance on any of these tasks. Though surprising, the absence of these expected relationships may be a result of the lower severity of amotivation in a non-clinical sample, which may not translate into impairments across all facets of the motivation system.

Based on studies in patients with schizophrenia, we hypothesized that participants with higher levels of subclinical schizotypal traits would demonstrate impaired reward expectancy and effort valuation. In our regression models, schizotypal traits were not predictive of motivation task performance. Correlational analyses, however, did reveal a significant inverse relationship between negative schizotypal traits and reward responsiveness, such that higher negative schizotypy was associated with lower IAPS ratings for both pleasantness and arousal. These findings are in line with other studies that have demonstrated a relationship between overall negative symptoms and pleasure in non-clinical samples (Chan et al., 2012; Fervaha et al., 2015c; Gard et al., 2006).

The limited number of published studies examining other facets of motivation in schizotypal populations makes comparisons with our findings challenging. The only study to our knowledge investigating effort valuation (EEfRT task performance) in a non-clinical sample found that individuals with elevated social anhedonia (who also reported elevated negative schizotypal traits) demonstrated increased effort choices particularly in medium probability trials (McCarthy et al., 2015). Our finding that higher schizotypal traits were significantly correlated with more effortful choices on the EEfRT are somewhat consistent with these previous findings, although in our sample this appeared to be driven by increased
effort choices at the high probability level. Another study using a probabilistic reward task revealed a trend towards elevated response bias, suggestive of increased propensity towards rewarding stimuli, in individuals with high schizotypy versus those with low schizotypy (Yan et al., 2011). While our findings may suggest better performance, taken together they may also reflect alterations in reward-based decision-making that could be connected to impaired salience attribution that has been posited to occur in schizophrenia (Kapur, 2003). Here, however, salience aberrations at the subclinical range of the spectrum may result in paradoxical increases in reward and effort-based decision-making.

In the current study, we also hypothesized that participants greater in subclinical depression would demonstrate deficient reward responsiveness and reward valuation, in keeping with findings in MDD. Our results partially supported these hypotheses, such that depressive symptoms significantly predicted self-reported anticipatory pleasure scores on the TEPS. These results align with other studies finding a reduction in anticipatory pleasure in individuals with subsyndromal depression (Yang et al., 2014). Further, a study by Liu et al. (2011) found differential reward processing impairments between individuals with subclinical and clinical depression. Specifically, impaired performance on a probabilistic reward learning task was driven by deficits in anticipatory pleasure for individuals with subclinical depression, whereas for clinically depressed patients, this deficit was related to reductions in consummatory pleasure (Liu et al., 2011). Thus, it may be that deficits in consummatory pleasure emerge with the more severe depressive symptoms accompanying a formal diagnosis of major depressive disorder.
Correlational analyses between objective motivational measures were conducted to explore inter-task relationships in order to further our understanding of the underlying mechanisms guiding performance on these tasks. Of note, discounting rates for small delayed rewards was related to effort valuation on the EEfRT. This finding supports the conceptualization that both reward and effort valuation serve to inform overall cost-benefit analyses in the context of rewards and goals. Further, our results revealed that both consummatory and anticipatory pleasure were correlated with IAPS pleasantness ratings for positive images, but only anticipatory pleasure was correlated with arousal ratings. Thus, the capacity for emotional arousal in the context of pleasant stimuli, in addition to in-the-moment feelings of pleasure, may promote the anticipation of future pleasurable events. Taken together, these findings lend support to the construct validity of the TEPS and its differentiation of in-the-moment versus anticipated pleasure. Further, the limited inter-correlations across other tasks suggest they each tap into different facets of the motivation system.

There are a few limitations to this study that warrant mention. First, our study sample consisted entirely of relatively young university students limiting the generalizability of these results to older populations. In addition, although participants were excluded if they reported a history of a schizophrenia-spectrum disorder, this was not confirmed with a structured diagnostic interview. Further, although we utilized objective measures of the motivation system, and administered the DCT in order to minimize non-credible responding secondary to poor effort, the subjective nature of symptom test measures serve as another limitation of this study. Finally, the comprehensive evaluation of discrete facets that comprise the motivational system would benefit from inclusion of multiple reward-based tasks believed to
tap into overlapping constructs, although to our knowledge the present investigation represents the most extensive to date.

The findings of the present study suggest that objective impairments across facets of the motivation system are driven primarily by variations in amotivation, rather than by schizotypal or subclinical depressive symptoms more broadly. Moreover, amotivation in this non-clinical sample appears to be driven by deficits in subjective and objective reward responsiveness. The absence of impairments in other facets of motivation, however, may be a reflection of the lower overall amotivation in this sample, with more widespread deficits emerging in clinical populations that experience more severe amotivation. Overall, our findings align with recent dimensional approaches to understanding core domains of psychopathology, and highlight the need for continued comprehensive evaluations of the motivation system across traditional diagnostic categories.
Chapter 5

Chapter 5: A dimensional examination of motivation system impairments in schizophrenia and major depressive disorder

5.1 Abstract

Importance: Motivation deficits are prevalent in schizophrenia and major depressive disorder. Often associated with poor functional outcomes, their alleviation remains an unmet therapeutic need. In spite of their transdiagnostic presence, there have been limited dimensional investigations of motivation system impairments across traditional diagnostic boundaries.

Objective: To systematically examine the multi-faceted motivation system in schizophrenia, major depressive disorder, and healthy participants using objective computerized measures.

Design, Setting, and Participants: Cross-sectional study conducted at the Centre for Addiction and Mental Health in Toronto, Canada. The study sample consisted of 39 patients with schizophrenia, 38 patients with major depressive disorder, and 39 healthy controls.

Interventions: Clinical amotivation was evaluated using the Apathy Evaluation Scale, followed by an extensive battery of objective measures of discrete facets of the motivation system.

Main Outcomes and Measures: Principal components analysis was conducted to examine the factor structure of motivation task performance, and multivariate hierarchical regression to
evaluate the roles of clinical amotivation on objective performance across facets of motivation. Subsequently, K-means clustering was used to identify subgroups of individuals with similar motivation profiles across the entire sample, with multivariate analyses of variance to investigate differences across facets of motivation and clinical measures between clusters.

Results: Principal components analysis revealed five motivation system factors representing: hedonic capacity; reward expectancy and learning; cost-benefit decision-making; goal-directed decision-making; and effort expenditure. Hierarchical regression revealed a significant effect of clinical amotivation ($p<.001$). Cluster analysis revealed 2 clusters of motivation performance, with cluster 1 characterized by lower hedonic capacity, and cluster 2 performing worse in cost-benefit and goal-directed decision-making, and effort expenditure. Each diagnostic group was represented in both clusters, though with significantly different distributions between clusters.

Conclusions and Relevance: Across SZ, MDD, and HC participants, this dimensional investigation revealed five underlying facets of the motivation system. Further, two clusters of motivation system profiles were found, but with diagnostic overlap highlighting the heterogeneity of clinical amotivation. These profiles of motivation system impairment may represent unique underlying patterns of neurobiological impairment, and may afford opportunities for novel treatments that address these deficits across diagnostic boundaries.
5.2 Introduction

Motivation deficits, or more specifically, the diminished ability to initiate and/or sustain goal-directed behaviour, are prevalent in schizophrenia (SZ) and major depressive disorder (MDD), and have been linked to poor functional outcomes in affected individuals. Amotivation has been shown to be the single most reliable predictor of functional impairments in schizophrenia (Fervaha et al., 2015a; Foussias et al., 2009; Kiang et al., 2003; Konstantakopoulos et al., 2011). Similarly, emerging work in major depressive disorder has also posited that the loss of motivation (which includes anhedonia) drives poor functional and treatment outcomes in these individuals (Fervaha et al., 2016b; Wells et al., 1989).

The importance of this transdiagnostic symptom has been recognized by the NIMH Research Domain Criteria (RDoC), which identifies approach motivation as a fundamental construct within the Positive Valence system. Within this broader construct, separate facets of motivation are articulated, including reward valuation, effort valuation, reward expectancy and action-selection/preference-based decision-making (Cuthbert and Insel, 2013). This definition aligns with the multi-faceted motivation framework proposed by Barch and Dowd (2010) whereby 1) hedonic capacity (i.e., “liking”) and 2) reward prediction (i.e., “wanting”, established through appropriate reward learning) converge to inform both 3) reward valuation and effort valuation (associated with a cost-benefit analysis), followed by the 4) development and implementation of an action plan to achieve the desired outcome.

To date, most studies examining motivation deficits have focused on isolated, discrete facets of motivation, often within a single neuropsychiatric disorder (Barch et al., 2016; Der-Avakian et al., 2015; Kring and Barch, 2014). While providing incremental and valuable
knowledge on the broader motivational deficits associated with these illnesses, such studies were not able to comprehensively examine the specific underlying mechanisms driving such impairments. Moreover, examining these facets across diagnostic boundaries and varying severity of motivational deficits may enable more precise characterizations of clinical amotivation, and aligns well with emerging dimensional approaches to understanding psychopathology.

Accordingly, the aim of this investigation is to objectively and comprehensively evaluate the facets of the motivational framework in a sample of SZ, MDD, and healthy participants. Further, we sought to identify subgroups of participants with similar motivation deficits across diagnostic groups. We hypothesized that the motivational framework would be comprised of 5 distinct facets: hedonic capacity, reward expectancy and learning, reward valuation, effort valuation and goal-directed decision making.

5.3 Materials & Methods

5.3.1 Participants

Participants recruited for this study consisted of 51 patients with SZ, 43 patients with MDD patients and 51 healthy controls (HC) between the ages of 18 and 55, matched for age, sex, and parental education as measured by the Barratt Simplified Measure of Social Status (BSMSS) (Barratt, 2006). Participants in the SZ and MDD groups met criteria for a DSM-IV diagnosis of SZ or schizoaffective (SA) disorder, or current MDD, respectively, as determined through the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1997). All SZ and MDD participants were stable outpatients with no changes in
treatment for at least 4 weeks. Patients were excluded if they: met diagnostic criteria for any other Axis I disorder (with the exception of an anxiety disorders for MDD patients); had a history of substance abuse or dependence in the past 6 months (with the exception of nicotine); a history of neurological disease; or were experiencing significant akathisia (global score of >2 on the Barnes Akathisia Rating Scale) (BARS; Barnes, 1989) or extrapyramidal symptoms (>2 on >2 items of the Simpson Angus Scale) (SAS; Simpson et al., 1970). HC participants were excluded if they met diagnostic criteria for any Axis I disorder, were taking psychotropic medication, or had a family history of a psychotic or mood disorder in a first-degree relative. The local research ethics board approved this study, and all participants provided written informed consent.

5.3.2 Clinical Assessments

Participants were administered a battery of clinical assessments including the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982), the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006), as well as the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) for SZ patients only. We specifically utilized the Apathy Evaluation Scale (AES; Marin et al., 1991) as our measure of clinical amotivation as it captures the behavioural, cognitive and emotional aspects of motivation, and does not rely solely on behavioural proxies. All participants were administered the Barratt Simplified Measure of Social Status (BSMSS; Barratt, 2006), the BARS, and the SAS, Lastly, the Brief Assessment of Cognition of Schizophrenia (BACS; Keefe et al., 2004) was administered to assess for cognitive functioning.
5.3.4 Objective measures of motivation

A battery of objective computerized tasks was also administered to assess for each facet of the motivation framework. Task administration was counterbalanced to minimize any order effects. Further, participants were informed that all monetary rewards were hypothetical, but were instructed to perform as if the reward was real. All computerized tasks were programmed and administered on Open Sesame v. 2.9.4 (Mathôt et al., 2012), with the exception of the ViPR and MCT which were programmed in a virtual reality rendering engine. Specific tasks are outlined below, with detailed methodology for each task provided in the Supplementary Methods.

Hedonic Capacity

The Evoked and Representational Responding Task (ERRT; Heerey and Gold, 2007), which incorporates images from the International Affective Picture System (IAPS; Lang et al., 1993) was administered to capture the “liking” and “wanting” components of hedonic experience. Specifically, the variables of interest for “liking” were pleasantness (IAPS-Pleasantness) and arousal (IAPS-Arousal) ratings for positive images, and click rate for positive images in the evoked condition (ERRT-Rate) for “wanting”. The ERRT has been used in two schizophrenia studies (Heerey and Gold, 2007; Lui et al., 2016), but to our knowledge has not been examined in the context of depression research. The IAPS, however, has been used extensively across many neuropsychiatric disorders, and is considered to be one of the most valid and reliable measures of in-the-moment pleasure (Jayaro et al., 2008).
**Reward Expectancy and Learning**

Reward expectancy (i.e. reward anticipation) was assessed using the Cued-Reinforcement Reaction Time (CRRT) task with the degree of reinforcement-related speeding (i.e. median reaction time for high probability trials minus median reaction time for low probability trials) as the variable of interest (Cools et al., 2005). Although the CRRT task specifically has been limited to schizophrenia samples (Mann et al., 2013; Murray et al., 2008; Roiser et al., 2009; Waltz et al., 2010), reward-related speeding paradigms more generally have been used in MDD (Forbes et al., 2009; Pizzagalli et al., 2009), as well as other disorders to assess for reward anticipation/expectancy. The Probabilistic Stimulus Selection (PSS) task was used to assess for reward learning, with PSS-Training score (calculated as percent correct in the last training phase divided by number of training phases), and proportion of trials correct for the A vs. Novel condition in the test phase (PSS-Test) as outcome variables (Frank, 2004; Waltz et al., 2007). The PSS has been used in a number of neuropsychiatric disorders such as schizophrenia and major depressive disorder as a measure of reinforcement learning (Frank, 2004; Waltz et al., 2007; Fervaha et al., 2013a; Whitmer et al., 2012).

**Reward Valuation**

Reward valuation was assessed using the Kirby Delay Discounting (DD) task, with the natural logarithm of the geometric mean of the discounting rate, k (Kirby-Avg) as the outcome variable (Kirby and Maraković, 1996). Delay discounting paradigms, including the Kirby task, is a widely used measure of reward valuation in both SZ (Ahn et al., 2011; Avsar
et al., 2013; Heerey et al., 2011, 2007) and MDD (Chung et al., 2017; Dombrovski et al., 2012; Pulcu et al., 2014).

**Effort Valuation**

Effort valuation was assessed using the Effort Expenditure for Rewards Task (EEfRT; Treadway et al., 2009) and the Virtual Progressive Ratio Task (ViPR; Foussias et al., 2013). The variables of interest were the proportion of hard trials chosen at the high probability level (EEfRT-High) for EEfRT, and task completions (ViPR-Tasks) and task completion rate (ViPR-Rate) for the ViPR task. The EEfRT task has been extensively used in SZ (Barch et al., 2014; Fervaha et al., 2013d; Treadway et al., 2015) and MDD (Sherdell et al., 2012; Treadway et al., 2012; Yang et al., 2016) as a measure of effort valuation (i.e. cost computation). The ViPR task, which was developed by our group as an ecologically valid measure of willingness to work, has only been used in schizophrenia (Foussias et al., 2013).

**Goal-directed Decision Making**

Goal-directed decision making was assessed using the Iowa Gambling Task (IGT) (Bechara et al., 1994) and the Multitasking in the City Test (MCT; Jovanovski et al., 2012). For the IGT, the variable of interest was the net score of advantageous minus disadvantageous card choices (IGT-Net), and for the MCT the distance travelled (MCT-Distance in virtual environment units) and MCT-Performance score (tasks completed - omission errors - commission errors). The IGT is one of the most common measures of reward-driven decision making, and has been extensively used in a number of neuropsychiatric populations, including SZ (Sevy et al., 2007; Shurman et al., 2005) and MDD (Cella et al., 2010; Must et al., 2006; Smoski et al., 2008). The MCT has been used by
our group in schizophrenia (Siddiqui et al., 2015), but to our knowledge, has not been utilized in a clinically depressed sample.

5.3.5 Analyses

The final sample with complete data across all tasks that could be included in the subsequent analyses consisted of 39 SZ patients, 38 MDD patients, and 39 HCs. Group differences in demographic and clinical variables were assessed using chi-square tests and analyses of variance (ANOVA), as appropriate. To investigate the factor structure of the motivation framework, an exploratory principal component analysis (PCA) using an oblique rotation (direct oblimin) was conducted on IAPS-Pleasantness, IAPS-Arousal, ERRT-Rate, Kirby-Avg, CRRT-RRS, PSS-Training, PSS-Test, EEfRT-High, ViPR-Rate, ViPR-Tasks, IGT-Net, MCT-Distance, and MCT-Performance across the entire sample. Factors were retained based on eigenvalues greater than 1, and regression-based factor scores were then computed to represent each facet of motivation which were used in all subsequent analyses. A multivariate hierarchical regression, with factor scores as the dependent variables and AES total score entered into the first step, followed by diagnostic group into the second step was conducted in order to determine the predictive value of amotivation and diagnosis on motivation task performance. To assess the effect of diagnostic group, two contrast codes were computed to represent SZ and MDD vs. HC, and SZ vs. MDD. In addition, K-means clustering following MacQueen’s (1967) methodology was conducted on the regression based factor scores to identify subgroups of individuals with similar motivation performance profiles across the entire sample (MacQueen, 1967). The optimal number of clusters was determined using the “nbclust” package which provides 30 indices for determining the number of clusters across different distance measures and clustering methods (Charrad et al., 2014).
Further, the consistency of the cluster solution was verified by establishing consensus with other clustering methods (i.e. hierarchical clustering). Demographic and clinical differences between clusters were examined using independent samples t-tests. Further, a multivariate analysis of variance (MANOVA) was conducted to evaluate cluster differences on motivation task performance. This analysis was repeated to control for the effects of age, cognition, as well as medication status which was entered as two binary contrasts: treatment with antipsychotic medication (antipsychotic vs. no antipsychotic), and antidepressant medication (antidepressant vs. no antidepressant).

All statistical tests were undertaken with the Statistical Package of Social Science (SPSS) version 24, with the exception of the cluster analysis which was undertaken using the “fpc” package version 2.1-10 (Henning, 2015) in R version 3.3.3 (R Core Team, 2016).

5.4 Results

5.4.1 Participant demographic and clinical characterization

The demographic and clinical characteristics of participants are shown in Table 5-1. Groups did not significantly differ in age, sex or parental education. However, the SZ group had significantly fewer years of education compared to both the MDD and HC groups.
<table>
<thead>
<tr>
<th></th>
<th>SZ</th>
<th>MDD</th>
<th>HC</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>33.6 (9.8)</td>
<td>31.8 (11.2)</td>
<td>30.3 (10.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>18:21</td>
<td>16:22</td>
<td>21:18</td>
<td>ns</td>
</tr>
<tr>
<td>Education**</td>
<td>15.0 (3.6)</td>
<td>16.7 (2.5)</td>
<td>17.2 (2.7)</td>
<td>HC=MDD &gt;SZ</td>
</tr>
<tr>
<td>Duration of Illness</td>
<td>11.2 (7.4)</td>
<td>12.3 (9.3)</td>
<td>-</td>
<td>ns</td>
</tr>
<tr>
<td>Parental Education</td>
<td>15.2 (5.6)</td>
<td>15.6 (4.6)</td>
<td>16.8 (4.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Diagnosis (SZ:SA)</td>
<td>:</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Medication (Yes:No)</td>
<td>39:0</td>
<td>26:12</td>
<td>-</td>
<td>ns</td>
</tr>
<tr>
<td>Antipsychotics (n)</td>
<td>31</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antidepressants (n)</td>
<td>0</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antipsychotics +</td>
<td>8</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antidepressants (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AES***</td>
<td>39.2 (6.6)</td>
<td>37.2 (4.7)</td>
<td>25.6 (4.8)</td>
<td>MDD=SZ &gt;HC</td>
</tr>
<tr>
<td>SANS Dim Exp***</td>
<td>10.6 (9.0)</td>
<td>3.8 (5.5)</td>
<td>0.9 (1.9)</td>
<td>HC&lt;MDD&lt;SZ</td>
</tr>
<tr>
<td>SAPS</td>
<td>23.5 (16.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HDRS***</td>
<td>10.5 (5.0)</td>
<td>16.9 (4.8)</td>
<td>2.0 (2.0)</td>
<td>HC&lt;SZ&lt;MDD</td>
</tr>
<tr>
<td>TEPS-Con*</td>
<td>4.4 (0.8)</td>
<td>4.1 (1.0)</td>
<td>4.6 (0.7)</td>
<td>HC &gt;MDD</td>
</tr>
<tr>
<td>TEPS-Ant***</td>
<td>4.4 (0.8)</td>
<td>3.6 (0.9)</td>
<td>4.6 (0.6)</td>
<td>HC=SZ &gt;MDD</td>
</tr>
<tr>
<td>BACS Composite***</td>
<td>-1.7 (1.3)</td>
<td>-0.3 (0.9)</td>
<td>0.3 (1.1)</td>
<td>HC&gt;MDD&gt;SZ</td>
</tr>
</tbody>
</table>

Note: Group differences are significant at *p<0.05, **p<0.01, or ***p<0.001.

5.4.2 Principal Component Analysis

The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the analysis, KMO=.626, and Bartlett’s test of sphericity $\chi^2 (78)=281.73, p <.001$, indicated that correlations between items were sufficiently large for PCA. Based on the scree plot and the interpretability of factor loadings, five factors were extracted that accounted for 60.93% of the total variance (Table 5-2). Based on variable loadings, the first factor represented hedonic capacity, with the second factor representing reward expectancy and learning, the third factor cost-benefit decision making, the fourth goal-directed decision making, and the fifth factor representing effort expenditure.
### Table 5-2: Factor loadings for motivation task variables.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IAPS-Pleasantness</td>
<td>.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAPS-Arousal</td>
<td>.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRRT-RRS</td>
<td></td>
<td>-.77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-Test</td>
<td>.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirby-Avg</td>
<td></td>
<td></td>
<td>-.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEfRT-High</td>
<td></td>
<td></td>
<td></td>
<td>.70</td>
<td></td>
</tr>
<tr>
<td>PSS-Training</td>
<td></td>
<td></td>
<td></td>
<td>.49</td>
<td></td>
</tr>
<tr>
<td>IGT-Net</td>
<td></td>
<td></td>
<td></td>
<td>.51</td>
<td></td>
</tr>
<tr>
<td>MCT-Distance</td>
<td></td>
<td></td>
<td>-.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCT-Performance</td>
<td></td>
<td></td>
<td></td>
<td>.70</td>
<td></td>
</tr>
<tr>
<td>ERRT-Rate</td>
<td></td>
<td></td>
<td></td>
<td>.56</td>
<td></td>
</tr>
<tr>
<td>ViPR-Rate</td>
<td></td>
<td></td>
<td></td>
<td>-.81</td>
<td></td>
</tr>
<tr>
<td>ViPR-Tasks</td>
<td></td>
<td></td>
<td></td>
<td>.86</td>
<td></td>
</tr>
</tbody>
</table>

Note: Factor loadings less than 0.4 are not shown.

(Abbreviations – IAPS: International Affective Picture System; CRRT-RRS: Cued-Reinforcement Reaction Time Task-Reinforcement Related Speeding; PSS: Probabilistic Stimulus Selection task; EEfRT: Effort Expenditure for Rewards Task; IGT: Iowa Gambling Task; MCT: Multitasking in the City Test; ERRT: Evoked and Representational Responding Task; ViPR: Virtual Reality Progressive Ratio Task)
5.4.3 Hierarchical Regression

The hierarchical multivariate regression revealed a significant main effect of amotivation in the first step ($F(5,110)=6.777$, $p<.001$), specifically predicting hedonic capacity ($\beta=-.041$, $p<.001$), effort expenditure ($\beta=-.027$, $p=.016$) and goal-directed decision making ($\beta=-.033$, $p=.003$). The addition of diagnosis in the second step revealed a significant main effect for the SZ vs. MDD contrast ($F(5,108)=6.331$, $p<.001$) for hedonic capacity ($\beta=.051$, $p=.019$), cost-benefit decision making ($\beta=-.521$, $p=.022$) and goal-directed decision making ($\beta=-.914$, $p<.001$), such that SZ patients performed significantly better than MDD patients on hedonic capacity, but worse on cost-benefit decision making and goal-directed decision making. There was no main effect for the SZ and MDD vs. HC contrast. Moreover, after including diagnostic group in the model, the main effect of AES ($F(5,108)=4.583$, $p=0.001$) remained significant only for hedonic capacity ($\beta=-.063$, $p<.001$).

5.4.4 Cluster Analysis

The k-means clustering algorithm provided a 2 factor solution with 75 participants assigned to cluster 1 and 41 to cluster 2. The consistency of the cluster solution was verified using hierarchical clustering which revealed an 85% overlap between the two methods. The motivation performance profiles of the 2 clusters are shown in Figure 5-1. Significant group differences suggest that cluster 1 is characterized by impaired hedonic capacity, whereas cluster 2 is characterized by impaired cost-benefit decision making, goal-directed decision making, and effort expenditure (Table 5-3). The clusters did not significantly differ on reward expectancy and learning performance. Furthermore, as shown in table 5-3, clusters did not significantly differ by sex, duration of illness, consummatory or anticipatory pleasure,
or severity of depression or clinical amotivation. However, cluster 2 was significantly more cognitively impaired compared to cluster 1 (Table 5-3). Controlling for the effects of cognitive functioning and medication status did not significantly change these results. Moreover, while the distribution of diagnoses was significantly different, all diagnostic groups were represented in each cluster (Figure 5-2).
Table 5-3: Demographic, clinical, and motivation performance characterization of clusters.

<table>
<thead>
<tr>
<th></th>
<th>Cluster Mean (SD)</th>
<th>1 (n=75)</th>
<th>2 (n=41)</th>
<th>t/χ²</th>
<th>p</th>
<th>Cluster Diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group (SZ:MDD:HC)</strong></td>
<td></td>
<td>17 : 29 : 29</td>
<td>22 : 9 : 10</td>
<td>11.4</td>
<td>.003</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sex (M:F)</strong></td>
<td></td>
<td>39:36</td>
<td>16:25</td>
<td>1.8</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td>28.2 (8.4)</td>
<td>38.7 (11.0)</td>
<td>-5.7</td>
<td>&lt;.001</td>
<td>1 &lt; 2</td>
</tr>
<tr>
<td><strong>Duration of Illness</strong></td>
<td></td>
<td>10.4 (8.0)</td>
<td>13.6 (8.6)</td>
<td>-1.7</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td><strong>Antipsychotics (%)</strong></td>
<td></td>
<td>25.3</td>
<td>58.5</td>
<td>12.5</td>
<td>&lt;.001</td>
<td>1 &lt; 2</td>
</tr>
<tr>
<td><strong>Antidepressants (%)</strong></td>
<td></td>
<td>26.7</td>
<td>34.1</td>
<td>0.7</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td>16.3 (3.0)</td>
<td>16.2 (3.2)</td>
<td>.12</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td><strong>AES</strong></td>
<td></td>
<td>33.2 (7.9)</td>
<td>35.4 (8.3)</td>
<td>-1.5</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td><strong>HDRS</strong></td>
<td></td>
<td>9.3 (7.6)</td>
<td>10.5 (7.0)</td>
<td>-0.8</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td><strong>TEPS-Con</strong></td>
<td></td>
<td>4.4 (0.8)</td>
<td>4.3 (0.8)</td>
<td>0.8</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td><strong>TEPS-Ant</strong></td>
<td></td>
<td>4.2 (1.0)</td>
<td>4.2 (0.7)</td>
<td>-0.3</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td><strong>BACS Z-score</strong></td>
<td></td>
<td>-0.04 (1.1)</td>
<td>-1.5 (1.3)</td>
<td>6.4</td>
<td>&lt;.001</td>
<td>1 &gt; 2</td>
</tr>
<tr>
<td><strong>Hedonic Capacity</strong></td>
<td></td>
<td>-0.2 (1.0)</td>
<td>0.4 (0.9)</td>
<td>-3.7</td>
<td>&lt;.001</td>
<td>1 &lt; 2</td>
</tr>
<tr>
<td><strong>Reward Expectancy</strong></td>
<td></td>
<td>0.07 (0.9)</td>
<td>-0.1 (1.2)</td>
<td>1.0</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cost-Benefit Decision Making</strong></td>
<td></td>
<td>0.4 (0.9)</td>
<td>-0.7 (0.8)</td>
<td>5.9</td>
<td>&lt;.001</td>
<td>1 &gt; 2</td>
</tr>
<tr>
<td><strong>Goal-Directed Decision Making</strong></td>
<td></td>
<td>0.4 (0.7)</td>
<td>-0.8 (1.0)</td>
<td>7.3</td>
<td>&lt;.001</td>
<td>1 &gt; 2</td>
</tr>
<tr>
<td><strong>Effort Expenditure</strong></td>
<td></td>
<td>0.4 (0.8)</td>
<td>-0.7 (1.0)</td>
<td>6.3</td>
<td>&lt;.001</td>
<td>1 &gt; 2</td>
</tr>
</tbody>
</table>

Note: See Table 5-1 for abbreviations.
Figure 5-1: Motivation performance profiles across clusters. Significant differences are denoted by \(*p<0.05\), or \(**p<0.01\).
Figure 5-2: Proportion of diagnostic groups across clusters.
Of note, participants in cluster 2 were also significantly older than those in cluster 1. Moreover, across the entire sample, age was correlated with hedonic capacity, goal-directed decision making and effort expenditure. Within cluster 1, age was not correlated with any of the facets of motivation; but in cluster 2, age was correlated with effort expenditure. Although controlling for the effects of age did not significantly change our results, we took additional steps to ensure that the impairments seen in cluster 2 were not entirely driven by the notable age difference between clusters. Specifically, we repeated the cluster analysis in a subsample of younger participants between the ages of 18 and 35 (n=77). In line with the aforementioned results, we identified a two cluster solution with cluster 2 characterized by significant impairments in reward expectancy and learning, goal-directed decision making, and effort expenditure compared to cluster 1 (See Supplementary Results: Figure 5-3). Importantly, however, the two clusters did not significantly differ in age, suggesting that the motivation impairments seen in cluster 2 cannot be exclusively attributed to the effects of age (See Supplementary Results: Table 5-4).

5.5 Discussion

The present study sought to systematically investigate the multi-faceted motivation framework across patients with schizophrenia and major depressive disorder, and healthy individuals. As per the proposed hypotheses and in line with emerging dimensional approaches to understanding psychopathology, however, we examined the reward and motivation system beyond diagnostic boundaries. To date, conceptualizations of the motivational framework have been based on the findings of individual studies investigating
isolated facets; however, no single study has yet to interrogate the discrete facets of motivation concurrently in SZ and MDD. Utilizing a comprehensive battery of objective test measures, our results revealed a five-factor structure of motivation comprised of 1) hedonic capacity, 2) reward expectancy and learning, 3) cost-benefit decision making, 4) goal-directed decision making, and 5) effort expenditure. These findings align well with the RDoC Positive Valence System (Cuthbert and Insel, 2010), as well as with the 4 component framework outlined by Barch and Dowd (2010), although there are some notable differences. Specifically, we identified an additional component representing effort expenditure, separate from both cost-benefit, and goal-directed decision making. Thus, we propose a framework in which hedonic capacity (“liking”) and reward expectancy (“wanting”) serve to inform cost-benefit decision-making (the convergence of reward and effort valuation), leading to a goal-directed decision, or the development and implementation of an action plan to achieve a desired outcome. The emergence of effort expenditure as a separate facet of motivation suggests that this may serve as a final step, whereby continuous re-evaluation and updating of value and cost representations may dynamically inform willingness to continue expending effort while in pursuit of a goal. In other words, hedonic capacity, reward expectancy and learning, and cost-benefit decision-making may be more relevant to the initiation of goal-directed behaviour, with effort expenditure involved in sustaining the motivation to achieve this final goal.

The results of our regression analyses revealed that clinical amotivation significantly predicted overall motivation task performance, particularly hedonic capacity. Further, this effect was independent of the influence of diagnosis, suggesting that differential motivation impairments may be driven by individual differences in amotivation severity. These results
also align well with a study by our own group suggesting that deficits in the subjective experience of pleasure are primarily driven by individuals with more severe amotivation, with our results extending these findings to objective test measures, as well (Da Silva et al., 2017). Moreover, the absence of a main effect for the patient vs. healthy control contrast lends further support for a dimensional approach to examining motivation on a continuum, rather than exclusively relying on traditional categorical comparisons.

In line with this dimensional approach, we sought to classify individuals – regardless of diagnosis – according to motivation performance. Our findings revealed two clusters of individuals with differential motivation profiles. Of note, individuals did not simply cluster by diagnosis. Rather, there emerged substantial overlap of SZ, MDD, and HC participants across clusters. While there were significantly more patients with SZ than MDD or HC participants in cluster 2, the number of SZ, MDD, and HC participants was relatively equal in cluster 1. Perhaps more interesting was the even distribution of patients with SZ across the clusters, which underscores the heterogeneous nature of the clinical presentation of motivational deficits in SZ. Indeed, these findings may shed some light on the source of discrepant findings across studies (Barch et al., 2016), with categorical diagnostic comparisons potentially too crude a method to capture individual differences within groups. In contrast, clustering individuals based on objective motivation performance may provide an alternative, more nuanced approach to understanding motivational impairments as they manifest in SZ and MDD. In the current study, we identified a cluster of individuals characterized by a specific impairment in hedonic capacity, but intact performance in all other motivation facets, and a second cluster with impaired cost-benefit decision making, goal-directed decision making, and effort expenditure, despite intact hedonic capacity.
Despite this clear distinction, however, the two clusters did not significantly differ in severity of clinical amotivation. This is particularly important as it suggests that differential impairments in one or more components can equally contribute to the clinical presentation of motivational deficits. Moreover, our findings align well with the existing literature suggesting differential neurobiological underpinnings across discrete facets of the motivation system. Specifically, consummatory anhedonia, the defining feature of the first cluster, has been linked to serotonergic or opiodic systems in the nucleus accumbens (Berridge, 2007; Smith and Berridge, 2005), with some evidence for a ventral striatal signal (Dowd and Barch, 2010). Conversely, impairments in higher-order reward processing, as seen in cluster 2, have been linked to dopaminergic dysfunction in striatal and cortical regions of the brain (Berridge and Robinson, 1998; Schultz, 2002; Wise, 2002). This distinction has important implications for the development of treatments targeting specific motivation deficits.

The present study has several strengths worth mentioning. To our knowledge, this study was the first to systematically examine the multi-faceted motivation system, and dimensionally investigate these facets concurrently in SZ, MDD, and HCs. Moreover, we utilized a comprehensive and extensive battery of objective computerized tasks, specifically intended to tap into the discrete facets of motivation. This being said, the findings of this study should be interpreted within the context of the following limitations. First, patients with SZ and MDD were being treated with different medications including antipsychotics, antidepressants, stimulants or some combination of the three. Unfortunately, there is currently no standardized method of calculating dose equivalences across different medication classes, which hinders our ability to directly evaluate the potential impact of medications across facets of motivation. While controlling for medication status did not
change the results of our analyses, we recognize the need for more sophisticated methods to determine the precise effects of medication. Additionally, future studies should aim to replicate these findings in medicated and non-medicated individuals. Second, there are no standard guidelines or methods to identifying or defining clusters. Although the present study took additional steps to verifying the validity and stability of our cluster analyses, replication in larger and broader clinical samples will be important to enhance the strength of our findings.

In summary, our findings support a multi-faceted motivation framework comprised of five components: hedonic capacity; reward expectancy and learning; cost-benefit decision making; goal-directed decision making; and effort expenditure. Further, across the entire sample of SZ, MDD, and HC participants, two distinct clusters of individuals emerged, with differential motivation system impairments. Taken together, the findings of the current study suggest that the clinical presentation of motivation deficits, irrespective of diagnostic status, may be determined by unique profiles of impairment across separate facets of the motivation system. Such impairment profiles may represent unique underlying neurobiological impairments, and may be differentially responsive to specific interventions. Thus, parsing motivation deficits into their underlying behavioural and neurobiological profiles may afford opportunities for the development of novel interventions, thereby fulfilling a key domain of unmet therapeutic need.
5.6 Supplementary Methods

5.6.1 Objective computerized measures

Hedonic Experience and Reward Expectancy

1) Evoked and Representational Responding Task

The Evoked and Representational Responding Task (ERRT), developed by Heerey and Gold (2007) incorporates a subset of positive, neutral, and negative valence images\(^1\) (14 each) from the International Affective Picture System (IAPS) (Lang et al., 1993) to evaluate internal representations of reward coupled with behavioural output (Heerey and Gold, 2007). In the representational condition of the task, participants are first asked to rate an image for pleasantness and arousal on 9-point Likert scales. After making the two ratings for each image, participants are presented with the option to seek or avoid future presentations by repeatedly pressing the “m” and “n” keys if they wanted to see the image again, or “x” and “z” if they did not want to see the image again. In the evoked condition of the task, participants are shown a subset of the images they had previously seen (10 of each valence), with the opportunity to prolong or reduce the viewing time of each image by repeatedly pressing the “m” and “n” or “x” and “z” keys on the keyboard.

2) Cued-Reinforcement Reaction Time Task

The Cued Reinforcement Reaction Time (CRRT) task was used to assess for reward expectancy or “wanting”, whereby participants perform a rapid odd-one-out judgment on

\(^1\) IAPS stimuli used in the study included: 1052, 1120, 1300, 1390, 1450, 1560, 1602, 1620, 2270, 2304, 2360, 2370, 2480, 2490, 2495, 2590, 2722, 4598, 5779, 5891, 5920, 5950, 5971, 6260, 6560, 7325, 7640, 8030, 8080, 8160, 8180, 8185, 8370, 8400, 8490, 9001, 9210, 9220, 9250, 9280, 9331.
three circles (Cools et al., 2005). A red, blue, or yellow coloured frame was presented along with the stimulus, which cued the likelihood of receiving points, each with a different pseudorandom reinforcement schedule (90%, 50%, and 10%, respectively). For each of the 96 trials, participants are instructed press “<”, “>”, or “?” on a computer keyboard to indicate the odd-one-out as quickly as possible. On reinforced trials, participants are awarded 100 points for correct and fast responses, 1 point for correct and slow responses, and 0 points for incorrect responses. Fast and slow response times are individually calibrated by calculating cut-off scores based on mean RT minus standard deviation RT during an initial practice phase.

_Reward Learning_

1) Probabilistic Stimulus Selection Task

On the Probabilistic Stimulus Selection (PSS) task, participants are presented with three different stimulus pairs (AB, CD, and EF) of pictures of common objects (Frank, 2004; Waltz et al., 2007). During the training phase of the task, participants are informed that there are no absolute right answers, but that some pictures have a higher chance of being correct, and to choose the picture that was most correct. Feedback was provided after each trial according to a predetermined probabilistic schedule. For example, in the AB condition, choosing “A” was rewarded with correct feedback for 80% of the trials, and choosing “B” was rewarded for the remaining 20% of the trials. Similarly, choosing “C” during the CD conditions and “E” from the EF conditions led to correct feedback in 70% and 60% of trials, respectively. Thus, participants should learn to choose the most rewarded stimuli of the pairs.
(i.e. A, C, and E) during the training phase. Each training phase consisted of 20 randomly presented trials for each stimulus pair, and in order to proceed to the test phase, participants must meet learning criteria by selecting the rewarding stimulus 65%, 60% and 50% of the time for AB, CD and EF stimulus pairs, respectively, or complete 6 training blocks. During the test phase, the original three stimulus pairs are presented along with novel A and B pairings (eg. AD, BC). Participants are instructed to continue choosing the most correct answer; however, no feedback is provided. Thus, the test phase assesses whether participants are able to transfer previously learned reward association to novel stimulus pairs (i.e., choosing A vs. novel, or avoiding B vs. novel).

*Reward Valuation*

1) Kirby Delay Discounting Task

The Kirby Delay Discounting (Kirby DD) task evaluates preferences for amount of money over time (Kirby and Maraković, 1996). This monetary choice task consists of 27 questions where participants are asked if they would rather receive a smaller immediate reward or a larger delayed reward.

*Effort Valuation*

1) Effort Expenditure for Rewards Task

The Effort Expenditure for Rewards Task (EEfRT) is a measure of willingness to expend effort for monetary reward (Treadway et al., 2009). In this modified version
consisting of 51 trials, participants are presented with the choice of completing an easy or hard task, along with the amount of money they would win for each option, as well as the probability of receiving the reward upon task completion (12%, 50%, and 88%). Both tasks involve filling up a bar on the computer screen by pressing a button on the keyboard a certain number of times, with the easy task requiring significantly fewer button presses than the hard task. On the easy task, participants were given 7 seconds to fill up the bar by pressing the “B” button on the keyboard with the index finger of their dominant hand for the possibility of winning $1.00, whereas the hard task required participants to fill up the bar within 21 seconds using the pinky finger of their non-dominant hand, for rewards ranging from $1.24 to $4.21. Of note, button press criteria for both easy and hard tasks were individually calibrated at the beginning of the task to account for differences in motor speed. Specifically, the easy task criterion was calculated as 50% of the maximum practice click rate for the dominant hand, and the hard task criterion was set at 80% of the maximum practice click rate for the non-dominant hand.

2) Virtual Reality Progressive Ratio Task

The Virtual Reality Progressive Ratio task (ViPR) is an ecologically-valid measure of willingness to expend effort in pursuit of a goal. Participants are instructed to complete a series of common everyday tasks using a joystick at vending machines within stores in a virtual city to earn as many points as possible (Foussias et al., 2013). Utilizing a progressively increasing work-to-reward ratio, the required number of tasks increases exponentially in order to receive more points (i.e. 100) as the task goes on. The task lasts up to 10 minutes, although participants are free to stop any time they wish.
Goal-Directed Decision Making

1) Iowa Gambling Task

The Iowa Gambling (IGT) requires participants to choose a card from 4 decks across 100 trials (Bechara et al., 1994). All decks lead to a reward, but differ according to frequency and magnitude of losses. Further, decks A and B are advantageous such that they provided small immediate rewards, but small losses as well. In contrast, C and D are disadvantageous decks as they offered larger immediate rewards, but greater losses as well. Participants were instructed to win as much money as possible and were told that some decks were better than others. Each card selection was followed by feedback indicating how much money was won, if and how much money was lost, with net wins depicted on a bar at the top of the screen.

2) The Multitasking in the City Test

The Multitasking in the City Test (MCT) is a virtual reality task in which participants are asked to complete a series of pre-specified errands (e.g. buying stationary, attending a scheduled doctor’s appointment) within a virtual city using a joystick within a period of 15 minutes (Jovanovski et al., 2012). Further, in order to minimize the cognitive load, participants have an initial practice run whereby they can navigate freely within the virtual city to develop familiarity, are provided with a map of the virtual city to which they can refer throughout the task, and the list of errands remains on the screen throughout the task.
Analyses:

The subsequent analyses were conducted for ease of comparison to other studies examining isolated facets of motivation using traditional diagnostic comparisons.

Hedonic Capacity and Reward Expectancy

1) ERRT

To assess for group differences on IAPS pleasantness and arousal ratings, we conducted a 3 (group: SZ vs. MDD vs. HC) x 3 (valence: positive, neutral, negative) x 2 (rating: pleasantness, arousal) mixed model ANOVA.

To assess for motivational salience, we examined click rate as a behavioural proxy for wanting. First, slide valence was determined on an individual basis as in Heerey and Gold (2007), such that pleasantness ratings between 1 and 3 were classified as negative, 4-6 neutral, and 7-9, positive. Click rate per second was then calculated across each valence, and for both evoked and representational conditions. In the representational condition, click rate was calculated as total clicks divided by 2 seconds whereas for the evoked condition, total number of clicks was divided by the response time window per trial. A 3 (group) x 3 (valence: positive, neutral, negative) x 2 (condition: evoked, representational) mixed model ANOVA was subsequently conducted to assess for group differences.

2) CRRT

To examine reward anticipation, median reaction times (RT) were calculated across the three different reinforcement probabilities (10% vs. 50% vs. 90%). Inaccurate and invalid trials in which RT exceeded 2000 milliseconds were excluded from the analysis. A 3 (group)
x 3 (reinforcement probability) mixed model ANOVA was then conducted to evaluate for group differences. Reinforcement-related speeding (RRS), calculated by subtracting the median RT of the 10% probability trials from the median RT of the 90% trials, was dichotomized in a binary variable with 0 coded for RRS ≥ 0 (i.e. no speeding), and 1 for RRS < 0 (i.e. speeding). A chi-square was subsequently conducted to evaluate for differences in the proportion of individuals demonstrating RRS across diagnostic groups.

*Reward Learning*

1) PSS

Reward learning during the acquisition phase was assessed using a training score, calculated on an individual basis as the proportion of correct trials on the last training phase divided by total number of training phases. A one-way ANOVA, with training score as the dependent variable, and group as the independent variable was conducted to assess for group differences. Reinforcement learning as a function of reward and punishment was also examined using the proportion of correct trials for the A vs. Novel and B vs. Novel conditions of the test phase. Participants who did not meet learning criteria in the practice phase were excluded from this analysis. A separate MANOVA, with A vs. Novel and B vs. Novel scores as the dependent variables and group as the independent variable was conducted to evaluate for group differences.
**Reward Valuation**

1) Kirby DD

The geometric mean of the natural logarithm of the discounting parameter \(k\) was calculated as in Kirby (1996) for small, medium, and large delayed rewards. A 3 (group) x 3 (bin: small vs. medium vs. large) mixed model ANOVA was subsequently conducted to evaluate for group differences in reward valuation.

**Effort Valuation**

1) EEfRT

Willingness to expend effort was evaluated as the proportion of hard trials chosen across differing probability and reward conditions. Reward level was dichotomized to represent high (>\$3) and low (<\$3) magnitudes. Further, inflexible responders (i.e. those who never chose the hard option) were excluded from the analysis. A 3(group) x 3 (probability: 12%, 50%, 88%) x 2 (reward: low, high) mixed model ANOVA was then conducted to assess for group differences in effort valuation.

2) ViPR

Effort valuation was also assessed using task completion rate (calculated as total task time / total task completions) on the ViPR. An ANOVA with completion rate as the dependent variable, and group as the independent variable was conducted to evaluate for group differences.
Goal-Directed Decision Making

1) IGT

Goal-directed decision making was assessed using the IGT-Net variable, calculated as total advantageous minus total disadvantages card choices. A one-way ANOVA was conducted, with IGT-Net as the dependent variable, and group as the independent variable. A cumulative net score of total advantageous minus disadvantages choices was also calculated across 5 bins of 20 trials. A 3 (group) x 5 (bin) mixed model ANOVA was subsequently conducted to evaluate performance throughout the task.

2) MCT

Completion distance (in virtual environment units-VEU), and performance score (total tasks completed minus omission and commission errors) on the MCT were also used to examine goal-directed decision making. A MANOVA with completion distance and performance score as the dependent variables, and group as the independent variable was then conducted.

Medication Effects

In order to further explore the effects of medication, we computed a binary antipsychotic (antipsychotic vs. no antipsychotic), and antidepressant contrast (antidepressant vs. no antidepressant). A MANOVA was subsequently conducted to evaluate for differences across the 5 facets of motivation.
### 5.6.3 Results

#### 5.6.3.1 Age-restricted cluster analysis

Table 5-4: Demographic, clinical, and motivation performance characterization of age-restricted clusters.

<table>
<thead>
<tr>
<th></th>
<th>Cluster Mean (SD)</th>
<th>t / χ²</th>
<th>p</th>
<th>Cluster Diff.</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td></td>
</tr>
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<td>11 : 16 : 22</td>
<td>4.9</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>2 (n=28)</td>
<td>13 : 7 : 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex (M:F)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n=49)</td>
<td>28:21</td>
<td>0.1</td>
<td>ns</td>
<td>-</td>
</tr>
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<td>2 (n=28)</td>
<td>11:17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>24.7 (4.2)</td>
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</tr>
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<td>26.0 (5.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>16.4 (3.0)</td>
<td>1.7</td>
<td>ns</td>
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</tr>
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<td>1 (n=49)</td>
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<td>15.2 (2.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>7.1 (4.1)</td>
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</tr>
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<td>2 (n=28)</td>
<td>35.4 (8.6)</td>
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</tr>
<tr>
<td><strong>HDRS</strong></td>
<td>8.3 (7.5)</td>
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<td>ns</td>
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<td>10.2 (7.2)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>TEPS-Con</strong></td>
<td>4.4 (0.8)</td>
<td>1.2</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>1 (n=49)</td>
<td>4.2 (1.0)</td>
<td></td>
<td></td>
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<td>4.2 (1.0)</td>
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<tr>
<td><strong>TEPS-Ant</strong></td>
<td>4.2 (0.8)</td>
<td>1.0</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>1 (n=49)</td>
<td>4.0 (1.0)</td>
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<td>2 (n=28)</td>
<td>4.0 (1.0)</td>
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<tr>
<td><strong>BACS Z-score</strong></td>
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<td>3.4</td>
<td>.004</td>
<td>1 &gt; 2</td>
</tr>
<tr>
<td>1 (n=49)</td>
<td>-1.1 (1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (n=28)</td>
<td>-1.1 (1.6)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Hedonic Capacity</strong></td>
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<td>2.0</td>
<td>.055</td>
<td>-</td>
</tr>
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<td>-0.3 (0.9)</td>
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<tr>
<td>2 (n=28)</td>
<td>-0.3 (0.9)</td>
<td></td>
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</tr>
<tr>
<td><strong>Reward Expectancy</strong></td>
<td>0.5 (0.7)</td>
<td>6.6</td>
<td>&lt;.001</td>
<td>1 &gt; 2</td>
</tr>
<tr>
<td>and Learning**</td>
<td>-0.8 (0.9)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Cost-Benefit Decision</strong></td>
<td>0.07 (0.9)</td>
<td>0.8</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>Making**</td>
<td>-0.1 (1.2)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Goal-Directed Decision</strong></td>
<td>0.3 (0.9)</td>
<td>3.2</td>
<td>.002</td>
<td>1 &gt; 2</td>
</tr>
<tr>
<td>Making**</td>
<td>-0.4 (1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Effort Expenditure</strong></td>
<td>0.5 (0.7)</td>
<td>8.1</td>
<td>&lt;.001</td>
<td>1 &gt; 2</td>
</tr>
<tr>
<td>1 (n=49)</td>
<td>-0.9 (0.8)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2 (n=28)</td>
<td>-0.9 (0.8)</td>
<td></td>
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</tbody>
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See table 5-1 for abbreviations.
Figure 5-3: Motivation performance profiles across age-restricted (18-35) clusters.

Significant differences are denoted by *p<0.05, or **p<0.01.
5.6.3.2 Traditional Diagnostic Comparisons

Hedonic Capacity and Reward Expectancy

1) ERRT

The ANOVA for self-reported liking revealed a significant main effect of valence \((F(2,140)=201.939, p<0.001)\) and rating \((F(1, 141)=14.050, p<0.001)\) indicating that overall ratings differed between positive, neutral, and negative valences, and that images were rated as more arousing than pleasant. Further, there was a significant group by valence interaction \((F(4,282)=4.859, p=0.001)\), with post hoc analyses revealing a significant effect of arousal for positive images only \((F(2,141)=5.404, p=0.005)\), such that MDD ratings were significantly lower than both SZ and HCs. There was no significant rating by group interaction, or 3-way interaction (Figure 5-4).
Figure 5-4: Mean A) pleasantness and B) arousal ratings across valences for SZ, MDD, and HC groups. Group differences are significant at *p<0.05, and **p<0.01. Error bars represent standard error of the mean.

The ANOVA for motivational salience revealed a significant main effect of valence ($F(2,128)=81.953, p<0.001$; negative > positive > neutral) and condition ($F(1,129)=72.333, p<0.001$; representational > evoked). Further, our results revealed a significant valence by group ($F(2,128)=81.953, p<0.001$), but no condition by group or 3-way interaction. Post-hoc one-way ANOVAs revealed a significant group difference for neutral images in the
representational \( (F(2,136)=3.484, p=0.033) \) and evoked \( (F(2, 135)=9.668, p<0.001) \) conditions, and for negative images during the evoked condition \( (F(2, 135)=3.903, p=0.023) \). Specifically, SZ patients had higher click rates for neutral images in both conditions, and lower rates for negative images in the evoked condition (Figure 5-5).

Figure 5-5: Average click rate across valences, and diagnostic groups for the A) representational and B) evoked conditions. Group differences are significant at *\( p<0.05 \), and **\( p<0.01 \). Error bars represent standard error of the mean.
2) CRRT

The ANOVA revealed no significant main effect, such that reaction times did not differ across reinforcement probabilities. There were also no significant group by probability interaction ($p=0.8$) (Figure 5-6). Similarly, there was no significant difference in the proportion of participants demonstrating reinforcement-related speeding across diagnoses (Figure 5-7). Of note, accuracy was not significantly different between groups.

**Figure 5-6:** Median reaction time across reinforcement cues for SZ, MDD, and HC groups. Error bars represent standard error of the mean.

**Figure 5-7:** Proportion of participants demonstrating reinforcement-related speeding across diagnostic groups.
Reward Valuation

1) Kirby DD

The ANOVA revealed a significant effect of bin, such that participants discount the value of smaller delayed rewards more rapidly than medium and large rewards. We did not, however find a significant group by bin interaction ($p=.29$), suggesting that groups are discounting the value of future rewards at similar rates (Figure 5-8).

![Figure 5-8](image)

Figure 5-8: The geometric mean of the natural logarithm of the discounting parameter ($k$) across reward size, and diagnostic groups. Error bars represent standard error of the mean.
**Reward Learning**

1) PSS

The one-way ANOVA revealed a significant main effect of group \( (F(2,129)=4.105, p=0.019) \), such that HCs had a higher learning score compared to both SZ and MDD groups (Figure 5-9). In contrast, the MANOVA revealed no significant effect of group, suggesting that SZ, MDD, and HC participants demonstrated comparable reward- and punishment-driven reinforcement learning (Figure 5-10).

**Figure 5-9:** Training score across diagnostic groups. Group differences are significant at \(*p<0.05\), and \(**p<0.01\). Error bars represent standard error of the mean.
Effort Valuation

1) EEfRT

Groups did not significantly differ in overall effort indexed by total number of hard choices, or in the proportion of tasks successfully completed. There was, however a significant main effect of probability ($F(2,138)=173.201, p<0.001$) and reward level ($F(1, 139)=451.348, p<0.001$), such that participants chose significantly more hard tasks on the high probability, and high reward trials. We also found a significant reward by group interaction ($F(2,139)=5.845, p=0.004$), and a non-significant trend for a probability by group interaction ($p=0.08$). Post-hoc one-way ANOVAs revealed a significant difference for the high probability-high reward condition ($F(2,139)=3.830, p=0.024$) such that SZ patients were choosing significantly fewer hard tasks, compared to both MDD and HC participants (Figure 5-10: Proportion correct for A vs. Novel and B vs. Novel conditions across groups. Error bars represent standard error of the mean.)
Further, a trend emerged for low probability-low reward trials ($F(2,139)=2.991$, $p=0.053$), such that patients with SZ were choosing significantly more hard tasks compared to MDD and HC participants. The three-way interaction was not significant.

![Graph A: Low Reward Trials](image)

![Graph B: High Reward Trials](image)

**Figure 5-11:** Mean proportion of hard trials across differing probability conditions for A) low reward and B) high reward trials. Group differences are significant at *$p<0.05$*, and **$p<0.01$*. Error bars represent standard error of the mean.
2) ViPR

The ANOVA revealed a significant main effect of group \( (F(2,141)=3.680, p=0.028) \), such that participants with SZ were less willing to work for points in the face of increasing effort requirements compared to healthy controls only (Figure 5-12).

![Completion Rate Graph](image)

**Figure 5-12: Completion rate (total task time / total task completions) across diagnostic groups. Group differences are significant at *\( p<0.05 \), and **\( p<0.01 \). Error bars represent standard error of the mean.**
Goal-Directed Decision Making

1) IGT

The one-way ANOVA revealed a significant main effect of group, such that patients with SZ chose significantly more disadvantageous card choices compared to MDD and HC participants (Figure 5-13). The mixed model ANOVA revealed a main effect of bin 
\( F(4,139)=7.481, p<0.001 \) and trend for a group by bin interaction \( F(8, 280)=1.779, p=0.081 \). Post-hoc analyses revealed that patients with SZ chose more disadvantageous card choices compared to both MDD and HC participants across bins 2-5 (Figure 5-14).

![Figure 5-13: Net score (advantageous minus disadvantageous choices) across diagnostic groups. Group differences are significant at *p<0.05, and **p<0.01. Error bars represent standard error of the mean.](image)
Figure 5-14: Cumulative net score (advantageous minus disadvantageous choices) across bins, and diagnostic group. Group differences are significant at *$p<0.05$, and **$p<0.01$. Error bars represent standard error of the mean.

2) MCT

The MANOVA revealed a significant main effect of group ($F(4, 270)=7.624$, $p<0.001$) for both distance ($F(2,135)=16.151$, $p<0.001$) and performance score ($F(2,135)=6.310$, $p=0.002$). Specifically, patients with SZ travelled a greater distance (Figure 5-15), and completed goal-oriented tasks less efficiently (Figure 5-16) compared to MDD and HC participants.
Figure 5-15: Distance travelled (in virtual environment units) across groups. Optimal distance represents the shortest possible distance required to complete all tasks. Group differences are significant at *$p<0.05$, and **$p<0.01$. Error bars represent standard error of the mean.

Figure 5-16: Performance score (total tasks completed – omission and commission errors) across groups. Group differences are significant at *$p<0.05$, and **$p<0.01$. Error bars represent standard error of the mean.
Medication Effects

The MANOVA revealed a significant main effect for the antipsychotic contrast ($F(5,108)=8.550, p<0.001$) for goal-directed decision making ($F(1,112)=40.715, p<0.001$) and effort expenditure ($F(1,112)=4.754, p=0.031$), such that participants being treated with antipsychotic medications (AP) performed significantly worse compared to those not being treated with AP (Figure 5-17). There was no significant main effect for the antidepressant contrast (Figure 5-18).

Figure 5-17: Antipsychotic group differences across facets of motivation. Group differences are significant at *$p<0.05$, and **$p<0.01$. Error bars represent standard error of the mean.
Figure 5-18: Antidepressant group differences across facets of motivation. Error bars represent standard error of the mean.
Chapter 6

6. Discussion

6.1 Summary of Results

Anticipatory and consummatory pleasure deficits in schizophrenia – the role of clinical amotivation

The overarching goal of this thesis was to systematically deconstruct the motivation and reward system in schizophrenia. Current conceptualizations of motivation outline a multi-faceted framework comprised of four components: hedonic experience (“liking”), reward expectancy (“wanting”), cost-benefit decision making (i.e. value representation and effort computations), and goal-directed decision making (Dowd and Barch, 2010). Though anhedonia (i.e. hedonic experience deficits) has long been considered a core symptom of schizophrenia, this notion has recently been called into question. Thus, our first objective was to clarify the nature and extent of hedonic impairments in schizophrenia by examining consummatory and anticipatory pleasure in a large sample of schizophrenia and healthy control participants. Moreover, given that hedonic capacity figures prominently within the broader motivation framework, we also sought to examine the relationship between consummatory and anticipatory pleasure, and severity of clinical amotivation. In line with our hypothesis, patients with schizophrenia and healthy controls reported comparable levels of in-the-moment consummatory pleasure. In contrast to our hypothesis, however, groups did not significantly differ in their levels of anticipatory pleasure. In reviewing previous investigations of the experience of pleasure in schizophrenia, we noted that studies reporting lower levels of anticipatory pleasure had higher proportions of patients being treated with
typical antipsychotics in comparison to our sample (Gard et al., 2007), and to others who failed to replicate these findings (Edwards et al., 2015; Cassidy et al., 2012; Strauss et al., 2011). Our results also revealed that amotivation severity significantly predicted consummatory and anticipatory pleasure, with no independent contribution of diagnostic group. Specifically, significant reductions in consummatory and anticipatory pleasure were primarily driven by individuals with more severe amotivation. Thus, these results offer some insight into the potential causes of discrepant findings across studies, with inconsistencies potentially driven by different distributions of clinical amotivation across diagnostic groups.

Investigation of motivation deficits in a non-clinical population – the roles of amotivation, depressive, and schizotypal symptoms

Recognizing the multiple facets comprising the motivation framework, we sought to expand our investigation beyond just hedonic experience. Specifically, our second aim was to examine the reward system utilizing objective measures of discrete facets of motivation in a non-clinical sample. The rationale for using a study sample comprised of undergraduate students, rather than patients, was to examine the role of subclinical depressive and schizotypal symptoms while minimizing illness-related confounds (i.e. medication class, illness chronicity) that may potentially affect motivation performance. In line with our hypothesis, severity of amotivation significantly predicted overall motivation task performance, and specifically in-the-moment IAPS ratings of pleasure and arousal, as well as self-reported consummatory and anticipatory pleasure. Surprisingly, however, amotivation severity did not predict performance across other objective facets of motivation, possibly
reflecting a continuum of impairment whereby more widespread impairments emerge with increasing severity of amotivation typically seen in clinical populations. Interestingly, EEfRT performance was positively correlated with SPQ scores, such that a higher level of schizotypy was associated with an increased willingness to expend effort in the 88% probability condition. Though surprising, we suggest the possibility that these findings may be a reflection of altered salience attribution related specifically to high probability trials. Aside from this relationship with EEfRT performance, subclinical depressive and schizotypal symptoms, as well as neurocognition did not significantly contribute to the prediction of overall motivation task performance, above and beyond self-reported motivational deficits. Taken together, these results align well with our first study, and extend the dimensional relationship between amotivation and subjective and objective hedonic experience to a non-clinical sample.

*Dimensional investigation of the motivation system across schizophrenia and major depressive disorder*

The objective of our final study was to systematically investigate the motivation framework concurrently across schizophrenia, major depressive disorder, and healthy control participants. Utilizing a comprehensive battery of objective computerized tasks, the results of our factor analysis revealed a multi-faceted motivation framework comprised of 5 distinct components: hedonic capacity, reward expectancy and learning, cost-benefit decision making, goal-directed decision making, and effort expenditure. These findings are somewhat in line with our hypothesis, with some notable exceptions. First, reward valuation and effort
valuation were subsumed under a single facet representing cost-benefit decision making, rather than emerging as separate components. Further, we identified an additional component representing the expenditure of effort that is independent of cost-benefit decision making and goal-directed action planning. Thus, we proposed a revised framework in which liking (i.e. hedonic capacity) and wanting (i.e. reward expectancy and learning) interact to inform reward valuations and effort computations (i.e. cost-benefit decision making), leading to the development and implementation of an action plan (i.e. goal-directed decision making), with the resultant goal-directed behaviour (i.e. effort expenditure) sustained through a dynamic process of re-evaluating and updating reward value and effort/cost requirements based on progress to the desired goal. This schematic is outlined in Figure 6-1.
Transitioning our examination of motivation deficits beyond traditional diagnostic comparisons towards a more dimensional approach, we conducted a cluster analysis in order to classify individuals based on motivation performance. Our results revealed an optimal 2 cluster solution, with unique motivation performance profiles. The first cluster of individuals exhibited impaired hedonic capacity, with intact performance across all other facets. In
contrast, the second cluster represented individuals with intact hedonic capacity, but impaired cost-benefit decision making, goal-directed decision making and effort expenditure. Drawing on previous neurobiological findings (Barch et al., 2016; Barch and Dowd, 2010; Der-Avakian et al., 2015; Treadway and Zald, 2011), the emergent clusters of individuals with unique motivation performance profiles suggests the possibility of distinct underlying neural mechanisms, with hedonic impairments seen in cluster 1 linked to altered opioidic or serotonergic systems, and cluster 2 impairments more closely related to dopaminergic dysfunction. Furthermore, perhaps most important to our dimensional investigation is that our cluster analysis did not classify individuals according to diagnostic status alone.

To date, however, most studies examining motivation have relied primarily on traditional diagnostic comparisons, often focused on isolated facets of motivation within a single illness population. In contrast, our study comprehensively examined facets of motivation more broadly across a sample of schizophrenia, major depression, and healthy control participants. For consistency with previous studies, we also conducted additional exploratory analyses using this traditional categorical approach. Our results revealed that SZ patients were significantly impaired in effort valuation, and goal-directed decision making compared to both MDD and HC participants. In contrast, SZ patients demonstrated comparable performance on measures of hedonic capacity (IAPS), reward expectancy (CRRT), and reward valuation (Kirby DD). Both SZ and MDD participants demonstrated impairments in rapid reward learning as measured by the PSS. Further, individuals in the MDD group demonstrated impairments on measures of hedonic capacity, compared to both SZ and HC groups. Though these findings are in line with some studies, our results are not consistent with all previous investigations. While our study, to our knowledge, is the most
comprehensive investigation of motivation deficits within and across diagnoses, the inconsistent diagnosis-specific findings highlight the challenges inherent to such investigations in heterogeneous disorders. Traditional diagnostic comparisons may simply be too crude a method to discover the true nature of motivation deficits across clinical populations. Indeed, the results of our dimensional analyses in study 3 suggest that differential proportions of patients sampled across motivation clusters may be driving the discrepant findings seen in previous studies.

Taken together, the findings of these three studies serve to advance our understanding of the phenomenology and behavioural underpinnings of motivation deficits in schizophrenia, major depressive disorder, and healthy controls. Our dimensional analyses offer important insights into the manifestation of amotivation across these groups, and highlight the need to move beyond a singular approach towards more comprehensive examinations of the motivation system. Going forward, parsing motivation deficits into their underlying behavioural and neurobiological profiles may allow for improved specificity, with opportunities to advance novel, more targeted treatment interventions.

6.2 Limitations

The studies presented in this thesis have several strengths worth mentioning. To our knowledge, our studies were the first to systematically examine the multi-faceted motivation system, and dimensionally investigate these facets across large clinical and non-clinical samples. Moreover, we utilized a comprehensive and extensive battery of objective computerized tasks, specifically intended to tap into the discrete facets of motivation. This
being said, the findings of these studies should be interpreted within the context of the following limitations. First, all schizophrenia patients were being treated with antipsychotic medications. Concerns have been raised regarding the influence of dopamine antagonism on motivation deficits, as well as the possibility that these symptoms are secondary to antipsychotic medications (Artaloytia et al., 2006; Mas et al., 2013). Further, antipsychotic class may also have profound effects on the reward and motivation system. For instance, neuroimaging and behavioural studies have demonstrated altered reward responses to anticipation cues and effort-cost computations in patients treated with typical antipsychotic drugs (Gold et al., 2015; Juckel et al., 2006a). Of note, however, a more recent study failed to show a significant association between antipsychotic medication and amotivation in schizophrenia (Fervaha et al., 2016a). Nonetheless, we took additional steps to minimize the potential effects of excessive dopamine antagonism by excluding individuals who exhibited significant extrapyramidal symptoms. In addition, we examined the relationship between antipsychotic dose, and clinical and objective measures of motivation, and included chlorpromazine equivalents as a covariate in our analyses, as appropriate.

Another important limitation to consider is the use of different psychotropic medications across diagnostic groups. In study three, for instance, patients were being treated with a variety of medications including antipsychotics, antidepressants, stimulants or some combination of the three. To date, however, there is no standardized method of calculating dose equivalences for different classes of drugs, which hinders our ability to make meaningful trans-diagnostic comparisons. In our analyses, we attempted to account for the effects of medication status by computing two binary contrasts: one for antipsychotics (i.e. antipsychotic vs. no antipsychotic), and one for antidepressants (antidepressant vs. no...
antidepressant), and including these as covariates in our analyses. In the supplementary section of this thesis, we further examined the specific roles of antipsychotic and antidepressant medication status on motivation task performance (of note, a similar contrast for stimulant medication status was not conducted due to the very small number of individuals using stimulant medication, thus precluding meaningful comparisons). Though we recognize that this may be a crude method that fails to capture the nuances of precise medication dosage effects, this approach has been used by others examining reward processes across diagnostic groups (Hägele et al., 2015). Future studies should aim to replicate these findings in both medicated and non-medicated samples in order to ascertain the effects of different medication class on motivation task performance.

Additionally, in study 1, anhedonia was assessed using only the TEPS, a self-rated scale that reports non-current feelings, and requires respondents to reliably recall and report on their experiences of pleasure. Recognizing the inherent restrictions of self-report questionnaires, as well as the discrepancies often noted between subjective and experiential measures, we sought to mitigate these limitations by incorporating objective measures in our investigations of the different motivation facets in studies 2 and 3. Moreover, clinical measures of negative symptoms, such as the SANS, are limited by their heavy reliance on behavioural proxies to evaluate amotivation. Although the SANS was administered, particularly to assess for diminished expression, we utilized the AES as our primary measure of amotivation in all 3 studies as it captures the behavioural, emotional, and cognitive aspects of this domain, without relying as heavily on functioning. Nonetheless, the subjective nature of clinical assessment and self-report serves as a limitation not only within these studies, but for the field of psychiatry more broadly. Moving forward, the development and incorporation
of objective assessments of clinical amotivation to augment clinical rating scales, and the inclusion of neuroimaging may enable the most comprehensive understanding of the human motivation system.

In our examination of the motivational framework in a non-clinical population, we utilized a sample comprised entirely of undergraduate students, limiting the generalizability of our results to the general population. Future studies should therefore aim to replicate these results in older healthy individuals. Moreover, all students received credit for participation, so it is possible that this method of recruitment biases studies examining motivation. Indeed, this selection bias can be applied to all research studies examining motivation. That is, the individuals partaking in these studies are at least motivated enough to voluntarily participate in these experiments.

Lastly, the third study utilized a clustering algorithm to identify subgroups of individuals with unique motivation performance profiles. The benefit of this approach is that it allows for a dimensional examination of the multiple facets of motivation beyond diagnostic boundaries. However, the drawback of cluster analyses is that results can vary depending on the choice of algorithm, distance functions and/or input data. Moreover, there are currently no guidelines for choosing the best clustering method, nor is there a gold standard for estimating the optimal number of clusters. Though we took additional steps to validate our results by computing a number of statistics, as well as establishing consensus with other clustering methods, these results require replication in a larger sample.
6.3 Future Directions:

Motivation deficits across neuropsychiatric disorders

The results of the studies presented here mark important steps forward in our understanding of motivational deficits, and guide future dimensional analyses of the multi-faceted motivation system. Given that this work is the first, to our knowledge, to comprehensively investigate the multiple facets of motivation in SZ, MDD, and HCs concurrently, future studies should aim to replicate our findings in a larger sample. Moreover, motivation deficits are not exclusive to schizophrenia or major depressive disorder, but exist in a number of other neuropsychiatric and neurological disorders including Alzheimer’s disease, Huntington’s disease and acquired traumatic brain injury. Thus, expanding the examination of specific motivational deficits to a broader range of illnesses is an important future direction that will serve to further our understanding of the differential manifestations of amotivation, but also enable further refinement of our proposed motivation framework and the interaction among discrete facets of motivation. An important direction going forward will be identifying motivation tasks that capture the core deficits of each cluster, or alternatively, developing a single computerized task that incorporates measures of both hedonic capacity, as well as higher-order reward system facets such as goal-directed decision making that will then allow for cluster profiling on the basis of task performance.

The interaction between motivation and cognition

Throughout this thesis, and across most studies of motivation deficits in clinical populations, neurocognitive functioning is routinely evaluated. This is driven by the
recognition that neurocognitive processes are closely related to, and likely support performance within specific facets of the motivation system. For example, working memory impairments have been found to contribute to more rapid discounting of delayed rewards in schizophrenia, with the suggestion that working memory is important for individuals to be able to maintain “online” representations of values or rewards (Gold et al., 2008; Heerey et al., 2011). Similarly, the processing of rapid reward learning and the utilization of this information for goal-directed decision making would be expected to rely on similar cognitive processes (Collins et al., 2014; Gold et al., 2008; Waltz et al., 2007). Conversely, overall motivation or effort that individuals exert during cognitive testing has been shown to contribute to deficits in cognitive test performance, although cognitive capacity for such individuals may be intact (Fervaha et al., 2014c; Foussias et al., 2015; Schmand et al., 1994). Although the findings in our studies were not impacted by differences in cognitive functioning across participants, there emerged relationships between facets of motivation (and clusters of motivation profiles) and global neurocognitive deficits. Moving forward, a more thorough investigation of the interaction of specific neurocognitive domains and their influence on facets of motivation, across clinical and non-clinical samples, would serve to deepen our understanding of motivation system functioning.

Importantly, while motivation tasks that are typically employed, including the ones described in this thesis, focus on abstract or inanimate stimuli and rewards, much of human existence involves the pursuit of goals in a social world. Social goals and rewards, however, comprise a domain of motivation that is often overlooked in studies of motivation. Further, while neurocognitive functions may be involved in motivation, an extended examination of the additional contributions of social cognition (i.e., mental processes underlying the ability
to perceive the intentions and feelings of others), would be particularly relevant given the growing awareness of social cognitive deficits in schizophrenia (Green et al., 2015), and the complex interplay between neurocognition, social cognition, and amotivation in predicting community functioning (Gard et al., 2009; Green et al., 2012; Sergi et al., 2007).

In light of the proposed dynamic process of updating reward value and cost requirements while in pursuit of a goal, it is also important to consider that the appraisal of “value” and calibration of “cost” is likely to change over time, as well. Such computations and decisions are likely influenced by the current clinical state of the individual, and also by the fundamental changes that occur in one’s environment as a result of developing a chronic or recurrent illness. Thus, an important area that remains underexplored is the longitudinal course of, and changes within the motivation system that are experienced by individuals in response to their illness. For example, the presence of dysfunctional attitudes, defeatist beliefs, and reduced expectations of reward or pleasure have been extensively documented in schizophrenia (Couture et al., 2011; Gard et al., 2007; Grant and Beck, 2009; Strauss and Gold, 2014), with the possibility that the motivational impairments observed in chronic illnesses may be a consequence of long-term disability, and the subsequent development of maladaptive cognitive biases about performance and ability (Rector et al., 2005). The extent to which such beliefs and expectations interact with the facets of motivation articulated in this thesis, as well as their developmental trajectory, are important questions for the future which may inform novel therapeutic strategies to address motivation impairments across clinical populations, and the optimal window within which to intervene.
The impact of psychotropic medications on the motivation system

With pharmacological interventions representing a clinical reality for patients with schizophrenia, major depressive disorder, and other neuropsychiatric disorders, it is also important to consider the influence of medication on clinical amotivation. As outlined above, antipsychotic medications have been linked to motivation deficits in some studies (Artaloytia et al., 2006; Mas et al., 2013), but not consistently (Fervaha et al., 2015b). Similarly, antidepressant medications have also been linked to motivation and hedonic impairments, with such impairments frequently listed as potential side effects from these medications, and in particular SSRIs (McCabe et al., 2010; Price et al., 2009). Unfortunately however, the current lack of standardized methods for calculating dose equivalences across different medication classes poses as a significant barrier to conducting meaningful transdiagnostic comparisons, and therefore warrants further investigation. One approach to evaluating the potential impact of psychotropic medications on the motivation and reward system could involve the examination of non-medicated samples and comparisons with medicated patient. An alternative strategy could involve pharmacologic challenge studies, whereby healthy participants receive acute and sub-acute administration of psychotropic medications (e.g., typical or atypical antipsychotic medication, serotonergic or noradrenergic antidepressant medication) with dose varied across participants, and serial evaluations of performance across facets of motivation.
Investigations of the neurobiology of the multi-faceted motivation system

To date, no single study has yet to comprehensively examine the neurobiological correlates of the multi-faceted motivation framework. Thus, our current understanding of the neurobiology of the reward system relies on individual studies examining isolated facets of motivation. According to the existing literature, hedonics (i.e. “liking”) is linked to the opioidic and gamma-aminobutyric acid-ergic (GABAergic) systems in the ventral striatum, nucleus accumbens and OFC (Dowd and Barch, 2010; Peciña et al., 2006; Smith and Berridge, 2007), whereas reward expectancy or anticipation (i.e. “wanting”) is associated with dopaminergic activity in the ventral striatal regions of the basal ganglia (Dowd and Barch, 2010; Knutson et al., 2008). Reward valuation, or the representation of value has been linked to lateral and medial OFC functions (Barch and Dowd, 2010; Gold et al., 2008), whereas the nucleus accumbens and anterior cingulate cortex have been implicated in effort-cost computations (Dowd and Barch, 2010; Salamone et al., 2003). Lastly, goal-directed decision making and planning has been linked to dorsolateral prefrontal cortex (DLPFC) (Barch, 2005; Semkovska et al., 2004). Though highly informative, these individual studies cannot address the extent to which specific brain regions are unique to each facet, or whether these are overlapping areas related to other motivation constructs. Thus, a more comprehensive examination of the neurobiological underpinnings of the motivation framework will allow for improved specificity, with the opportunity to uncover precise brain-behaviour relationships and the full range of motivation impairments across diagnoses.

Informed by these findings, we can then explore an avenue for target engagement in clinical trials that simulate or challenge the neural circuitry of these constructs in new clinical trial subgroups.
Perhaps most pertinent to the discussion of motivation deficits in clinical populations is its link to poor functional outcomes, and the unmet therapeutic need that it currently represents. The results of these studies suggest several potential novel therapeutic avenues worth pursuing. Pharmacologic and brain stimulation interventions for motivation deficits (or more broadly negative symptoms) have typically been carried out in schizophrenia populations, and have yielded inconsistent effects. Examination of results from meta-analyses, however, suggests that some patients do experience a benefit (Fusar-Poli et al., 2015; Singh et al., 2010). In light of our findings of distinct clusters, the characterization of individuals based on the underlying motivation profile driving their clinical amotivation may serve to identify the subgroups of patients who are more likely to benefit from a particular intervention. Similarly, non-pharmacologic interventions such as computerized cognitive remediation (Cella et al., 2017; Sánchez et al., 2014; Vita et al., 2011; Wykes et al., 2011), and early findings from our group on the use of virtual reality-based motivation training (Foussias et al., 2017), indicate potential benefit for negative symptoms and in particular motivation deficits. What remains unanswered is the extent to which a particular cluster of individuals is more responsive to such interventions based on their profile of motivation impairment. It will therefore be important for neurobiological investigations to uncover the neural mechanisms that give rise to unique clusters of motivation profiles in order to inform targeted therapeutic interventions based on region-specific brain stimulation or neurotransmitter-specific pharmacologic interventions. Finally, early identification of an individual’s behavioural and neurobiological motivation system profile may inform strategies.
for combining brain stimulation, pharmacologic intervention, and computerized brain training, with the ultimate goal of mitigating functional impairment and optimizing their functional recovery.

Conclusions

The findings across these three studies serve to further our understanding of the behavioural and neurobiological mechanisms underlying motivation deficits in schizophrenia and major depressive disorder. Our results suggest that clinical amotivation is a significant predictor of subjective and objective motivation performance in both clinical and non-clinical samples. Further, utilizing the most comprehensive and extensive battery of objective measures to date, our results revealed a motivational framework comprised of hedonic capacity, reward expectancy and learning, cost-benefit decision making, goal-directed decision making, and effort expenditure. In line with dimensional approaches to examining psychopathology, we identified 2 clusters of individuals with similar behavioural motivation profiles, and potentially distinct underlying neurobiological mechanisms across SZ, MDD, and healthy control participants. These findings may shed light on novel treatment opportunities targeting this domain of unmet therapeutic need.
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