Investigations Of The Determinants of Functional Outcomes In Schizophrenia: Cross-sectional And Longitudinal Examinations Of The Role Of Negative Symptoms

by

George Foussias

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Institute of Medical Science
University of Toronto

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Doctor of Philosophy
Institute of Medical Science
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2013

Abstract

Despite significant advances in the field, functional impairment continues to be a characteristic feature of schizophrenia. Negative symptoms, and in particular motivational deficits, along with cognitive dysfunction have consistently been linked with functional impairments in schizophrenia. However, most investigations of functional outcomes have focused on discrete symptoms, or alternatively on broad symptom domains. Further, recent findings have suggested that a lack of motivation may contribute to the cognitive impairment seen in schizophrenia. This series of investigations sought to: 1) advance our understanding of the determinants of cross-sectional and longitudinal community functioning in schizophrenia by examining the concurrent contribution of negative symptoms, cognition, and other important symptoms to longitudinal functioning in schizophrenia over one year; and 2) clarify the relationships between motivation, effort exerted during cognitive testing, and cognitive performance in schizophrenia. We hypothesized that: 1) motivational deficits would serve as the most important and stable determinant of community functioning, with cognition offering additional predictive value; and 2) motivational deficits would exhibit a differential relationship across various cognitive domains, with those exhibiting reduced effort during testing evincing more severe motivational
deficits. Seventy stable adult outpatients with schizophrenia or schizoaffective disorder underwent clinical, cognitive, and functional evaluations at baseline, 6 months, and 12 months. Using stepwise and hierarchical regression analyses, motivational deficits emerged as the most predictive and reliable determinant of cross-sectional and longitudinal community functioning, accounting for up to 58% of the variance in functioning. Other symptom domains exhibited substantially less predictive value for functioning. Motivational deficits also exhibited a differential relationship across cognitive domains, with a particular relationship with verbal fluency. Further, effort during cognitive testing appeared to be related to both cognitive dysfunction and motivation, suggesting that the use of performance validity tests in schizophrenia may not be an appropriate index of mental effort. Overall, these findings highlight the central role motivational deficits play in determining outcomes in schizophrenia, as well as their impact on cognitive dysfunction in this illness. Importantly, in spite of advances in treatment, this work points to the essential need for interventions to address these motivational deficits if we hope to improve outcomes in schizophrenia.
Acknowledgments

First, I would like to thank my PhD Supervisor, Dr. Gary Remington, for his tremendous support and mentorship throughout my doctoral work and development as a clinician-scientist. His thoughtful approach to supervision and mentorship inspires and promotes flexibility, broad thinking outside traditional boundaries or silos, and the development of independence in his students. He is always encouraging and supportive, and provides a wonderful learning environment in which his students are challenged to achieve to the maximum of their potential. I hope that I can offer to future generations of scientists and clinician-scientists this same excellence in mentorship that he has provided.

I would also like to thank the members of my PhD Advisory Committee, Dr. Konstantine K. Zakzanis and Dr. Rob van Reekum, whose support and encouragement has been unwavering. You have both instilled in me an appreciation for the diverse ways in which we can explore scientific questions, and understand the answers we find. I also thank Steve Mann, Carol Borlido, Ishraq Siddiqui, and Krysta McDonald for their support in recruitment, assessments, and logistics throughout this work. Importantly, I thank all the participants who volunteered to take part in this work.

To my loving family I cannot express how much your support throughout my life and career has meant. My mother and father, whose endless enthusiasm and encouragement has been a source of strength and motivation. I will eventually figure out how that train works. My brother, who is always supportive and curious about my work, and on whom I can always count on, I am grateful. I wish him, his wife, and their new baby girl Athanasia, a lifetime of happiness and success. I thank my wife Ariana for her boundless love, encouragement, and support at every step. To my beautiful daughter Agoritsa, now just over one year old, you have given me such happiness and joy, and a renewed fascination for how we learn from the world around us.

Finally, I thank both the Centre for Addiction and Mental Health, and the Canadian Institutes of Health Research, for their support of this work.
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<th>Description</th>
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<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>AES</td>
<td>Apathy Evaluation Scale</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike Information Criterion</td>
</tr>
<tr>
<td>BACS</td>
<td>Brief Assessment of Cognition in Schizophrenia</td>
</tr>
<tr>
<td>BNSS</td>
<td>Brief Negative Symptom Scale</td>
</tr>
<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>CAINS</td>
<td>Clinical Assessment Interview for Negative Symptoms</td>
</tr>
<tr>
<td>CDSS</td>
<td>Calgary Depression Scale for Schizophrenia</td>
</tr>
<tr>
<td>COA</td>
<td>Common Objects and Activities subscale</td>
</tr>
<tr>
<td>CPZ</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion tensor imaging</td>
</tr>
<tr>
<td>FGA</td>
<td>First generation antipsychotic</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma amino butyric acid</td>
</tr>
<tr>
<td>HD</td>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>HRSD-DS</td>
<td>Hamilton Rating Scale for Depression – Depressive Symptom factor</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
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<tr>
<td>HRSD-NS</td>
<td>Hamilton Rating Scale for Depression – Negative Symptom factor</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IR</td>
<td>Interpersonal Relations subscale</td>
</tr>
<tr>
<td>LE</td>
<td>Low effort</td>
</tr>
<tr>
<td>MATRICS</td>
<td>Measurement and Treatment Research to Improve Cognition in Schizophrenia</td>
</tr>
<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NAA</td>
<td>N-acetylaspartate</td>
</tr>
<tr>
<td>NE</td>
<td>Normal effort</td>
</tr>
<tr>
<td>NSA</td>
<td>Negative Symptom Assessment</td>
</tr>
<tr>
<td>NIMH</td>
<td>National Institute of Mental Health</td>
</tr>
<tr>
<td>NOS</td>
<td>Not otherwise specified</td>
</tr>
<tr>
<td>OFC</td>
<td>Orbitofrontal cortex</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
</tr>
<tr>
<td>PAS</td>
<td>Physical Anhedonia Scale</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
</tr>
<tr>
<td>PVT</td>
<td>Performance validity test</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>QLS</td>
<td>Quality of Life Scale</td>
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<tr>
<td>rCBF</td>
<td>Regional cerebral blood flow</td>
</tr>
<tr>
<td>Role</td>
<td>Instrumental Role subscale</td>
</tr>
<tr>
<td>SANS</td>
<td>Scale for the Assessment of Negative Symptoms</td>
</tr>
<tr>
<td>SANS-AD</td>
<td>Scale for the Assessment of Negative Symptoms – Alzheimer’s disease</td>
</tr>
<tr>
<td>SAPS</td>
<td>Scale for the Assessment of Positive Symptoms</td>
</tr>
<tr>
<td>SARS</td>
<td>Simpson Angus Rating Scale</td>
</tr>
<tr>
<td>SAS</td>
<td>Social Anhedonia Scale</td>
</tr>
<tr>
<td>SDS</td>
<td>Schedule for the Deficit Syndrome</td>
</tr>
<tr>
<td>SGA</td>
<td>Second generation antipsychotic</td>
</tr>
<tr>
<td>SPD</td>
<td>Schizotypal Personality Disorder</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>TEPS</td>
<td>Temporal Experience of Pleasure Scale</td>
</tr>
<tr>
<td>TLE</td>
<td>Temporal lobe epilepsy</td>
</tr>
<tr>
<td>TOMM</td>
<td>Test of Memory Malingering</td>
</tr>
<tr>
<td>VTA</td>
<td>Ventral tegmental area</td>
</tr>
<tr>
<td>WHO/PIRS</td>
<td>World Health Organization Psychological Impairments Rating Scale</td>
</tr>
<tr>
<td>WMT</td>
<td>Word Memory Test</td>
</tr>
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Chapter 1

Introduction

1.1 Schizophrenia: Historical Foundations

Historical accounts of schizophrenia often begin with reference to the detailed writings of the phenomenology and course of dementia praecox by Emil Kraepelin, and subsequently schizophrenia by Eugen Bleuler (Kraepelin 1919; Bleuler 1950). Examinations of historical writings dating back to the third millennium BC, however, reveal clinical descriptions of symptoms that align with contemporary notions of schizophrenia (reviewed in (Jeste, del Carmen et al. 1985). The earliest descriptions come from ancient Mesopotamia, which make reference to individuals being “persecuted by ‘mischief makers’ who resort to witchcraft, spells, magic, or ‘other evil machinations’” (Jeste, del Carmen et al. 1985). Ensuing writings in ancient Indian medicine from the 14th century BC describe individuals experiencing demonic possession, behavioural disorganization, and cognitive impairments. Writings from ancient Greece and Rome during the last 4 centuries BC and into the first century AD also detail peoples’ experiences of hallucinations, delusions, and disorders of judgment. Similar descriptions continued to arise in writings during the middle ages and into the fifteenth century, with an examination of the life history of King Henry VI of England revealing ‘a central poverty in his personality’ and a course of illness suggestive of chronic undifferentiated schizophrenia (Jeste, del Carmen et al. 1985). Further case descriptions by Platter in the seventeenth century make note of a range of delusions lasting for months to years, including lycanthropy (i.e., delusions of
being transformed into a wolf), as do several autobiographical accounts of psychotic symptoms that align with current nosological criteria for schizophrenia. During the same time, Thomas Willis, a physician better known for his discovery of the Circle of Willis in the arterial network in the brain, described a distinction between “foolishness” (schizophrenia) and “stupidity” (mental retardation) (Jeste, del Carmen et al. 1985).

By the 19th century there emerged within European psychiatry more systematic descriptions of patients presenting at a young age with symptoms consistent with what is now classified as schizophrenia. The French physician Benedict Morel was one of the earliest to use the term *dementia precoce* (i.e., premature dementia) in his descriptions of these patients (Morel 1860). Around the same time Thomas Clouston, a Scottish psychiatrist, described similar presentations as “adolescent insanity”, while the Czech neurologist and psychiatrist Arnold Pick, now famous for his identification of Pick bodies in cases of dementia, also used the Latin term *dementia praecox* in his writings (Kraepelin 1919). It was Emil Kraepelin in 1896, however, who first used the term *dementia praecox* to define a single nosological entity encompassing the varied clinical pictures of patients he followed longitudinally that presented with the constellation of symptoms that would inform future diagnostic criteria for schizophrenia (Kraepelin 1919). Importantly, he was also the first to distinguish *dementia praecox* from manic-depressive and other psychiatric illnesses, setting the stage for the current nosological systems used in psychiatry. Around the same time, Eugen Bleuler was conducting examinations of similar patients and used the term schizophrenia, in his clinical descriptions (Bleuler 1950). Importantly, while Kraepelin recognized the heterogeneity of clinical presentations and longitudinal course in this illness, Bleuler was more explicit in his writing about “the group of schizophrenias”, with the incorporation of differing clinical subgroups and longitudinal illness courses. Both Kraepelin and Bleuler however, appreciated the diverse constellation of symptoms of schizophrenia.
including psychosis (i.e., positive symptoms), disturbances of affect, volition, and relatedness (i.e., negative symptoms), as well as disorders of thought, speech, and behaviour (i.e., disorganization symptoms). Ensuing work by the German psychiatrist Kurt Schneider in the middle of the 20th century focused sharply on the psychotic symptoms of schizophrenia, with an attempt to delineate pathognomonic “first rank symptoms” of schizophrenia (audible thoughts, voices arguing or discussing, voices commenting on the patient’s actions, somatic passivity, thought withdrawal, thought insertion, thought broadcasting, made feelings, impulses, and acts, and delusional perceptions) (Schneider 1959). Due to both the clarity of his definition of these symptoms, in conjunction with the contemporaneous discovery of the first antipsychotic medication, chlorpromazine, and a shift in focus for the field towards treatment of psychosis, these first-rank symptoms became influential in the development of modern diagnostic criteria for schizophrenia.

1.2 Diagnosis, Epidemiology, and Risk Factors

Current diagnostic criteria for schizophrenia, outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD), have undergone several revisions over the past half-century. The most recent versions, DSM-IV-TR and ICD-10, have been in place for the past twenty years. Of note, a recent revision to DSM-5 has been released in the past month, with an upcoming revision to ICD-11 coming over the next year. As much of the contemporary work in schizophrenia has been based on DSM-IV diagnostic criteria, however, it is these criteria that are outlined below:
Table 1-1. DSM-IV-TR Diagnostic Criteria for Schizophrenia (American Psychiatric Association 2000)

<table>
<thead>
<tr>
<th>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):</th>
</tr>
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<tbody>
<tr>
<td>(1) delusions</td>
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<td>(2) hallucinations</td>
</tr>
<tr>
<td>(3) disorganized speech (e.g., frequent derailment or incoherence)</td>
</tr>
<tr>
<td>(4) grossly disorganized or catatonic behavior</td>
</tr>
<tr>
<td>(5) negative symptoms, i.e., affective flattening, alogia, or avolition</td>
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</tbody>
</table>

**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).

At the forefront of these diagnostic criteria stand the Schneiderian first-rank symptoms, reflecting their ongoing prominence within contemporary conceptualizations of schizophrenia,
along with symptoms of disorganization of speech and behaviour. Negative symptoms emerge as the final (A) criterion for the diagnosis of schizophrenia. This current conceptualization stands in stark contrast to the historical conceptualizations of this illness by Kraepelin and Bleuler, both of whom viewed psychotic symptoms as secondary or accessory symptoms, with a view that negative symptoms including disturbances of affect and volition represented the central features of schizophrenia (Kraepelin 1919; Bleuler 1950). The recently released revision to the diagnostic criteria for schizophrenia in DSM-5 moves somewhat closer to the Kraepelinian and Bleulerian view of schizophrenia symptomatology, at least with regards to negative symptoms, with a demarcation of diminished emotional expression (affective flattening and alogia) and avolition within the (A) criteria for negative symptoms (American Psychiatric Association 2013). Other diagnostic criteria remain essentially unchanged.

The availability of reliable diagnostic criteria has permitted valuable examinations of the epidemiology of schizophrenia across the globe. From this collective work spanning several decades, lifetime prevalence rates of schizophrenia range from 0.3% to 2%, with an average prevalence of 0.7% and annual incidence rates ranging from 8 to 40 per 100,000 per year (Tandon, Keshavan et al. 2008). Much of the variability in these estimates appears driven by higher incidence rates related to urbanicity, migration, socio-economic classes, and sex differences. Although it was initially believed that lifetime risk of developing schizophrenia was similar between among males and females, recent studies have revealed a somewhat higher risk in males (male-female relative risk of 1.4) (Tandon, Keshavan et al. 2008). There has also been a long-standing recognition of sex differences with regards to the onset of symptoms of schizophrenia. In general, the onset of psychotic symptoms typically occurs between late-teens and mid-30s, with a peak onset in males in their early- to mid-20s, and for females in their late-20s (American Psychiatric Association 2013). Further, while some individuals experience an
abrupt onset of symptoms, the majority of individuals experience a slow and gradually progressive prodromal phase, lasting from one month to several years. This early phase is frequently characterized by disturbances in motivation, emotional expression, cognition, mood, and functional impairment, and eventually attenuated psychotic symptoms (an der Heiden and Hafner 2000; Tandon, Nasrallah et al. 2009). Overall, established risk factors for the development of schizophrenia, listed in order of decreasing relative risk, including: family history of schizophrenia (monozygotic twins > both parents affected > dizygotic twin or 1st degree relative > 2nd degree relative > 3rd degree relative); urbanicity; migration; obstetric or perinatal complications; 1st or 2nd trimester maternal infection or malnutrition; cannabis or stimulant use; paternal age > 35 years; male gender; and winter birth (Tandon, Keshavan et al. 2008).

1.3 Treatment

Antipsychotic medications represent the cornerstone of treatment for schizophrenia. Prior to the discovery of antipsychotic medications in the 1950s, treatment consisted primarily of custodial care, with the provision of safe and supportive environments for patients within long-stay psychiatric institutions. Trials of various somatic treatments at the time included hydrotherapy, sedative agents for extreme agitation, insulin coma treatment, frontal lobotomy, and pharmacologic and electroconvulsive therapies, all of which offered questionable efficacy and were subsequently abandoned (Sadock, Sadock et al. 2009). The discovery of the calming effect of chlorpromazine in the early 1950s by Henri Laborit, a surgeon in Paris, and subsequently shown in a clinical trial in 1952 in acutely psychotic patients by Jean Delay and Pierre Deniker to have pronounced antipsychotic effects, revolutionized the treatment of schizophrenia (Sadock,
Sadock et al. 2009; Tandon, Nasrallah et al. 2010). A new era of treatment for schizophrenia began, and led to a reduction in the number of patients institutionalized in psychiatric hospitals around the world, and the development of a multitude of similar medications, subsequently classified as first- and second-generation antipsychotics (FGAs and SGAs, respectively) (Sadock, Sadock et al. 2009; Tandon, Nasrallah et al. 2010). Despite differences between medications, both in terms of chemical structure and affinity for dopamine D2 versus other receptors, investigations have revealed that antipsychotic activity is linked to their antagonism of the dopamine D2 receptor (Seeman 2002; Remington 2003). Moreover, recent large-scale effectiveness trials in the United States and the United Kingdom have revealed no difference in clinical effectiveness between FGAs and SGAs for the treatment of schizophrenia (Lieberman, Stroup et al. 2005; Jones, Barnes et al. 2006; Foussias and Remington 2010). The exception to this has been clozapine, which served as the prototype of “atypical” antipsychotics (SGAs) with its lower liability to induce extrapyramidal symptoms, and has emerged as the most effective antipsychotic agent for treatment-resistant schizophrenia (Kane, Honigfeld et al. 1988; Foussias and Remington 2010).

With the development of numerous SGAs, there emerged some initial hope that these newer agents would offer some benefit for the treatment of the symptoms of schizophrenia beyond psychosis, i.e., the negative and cognitive symptoms that have been increasingly recognized in schizophrenia (see below). Despite this early promise, however, accumulating evidence has suggested that SGAs, as well as FGAs, remain largely ineffective in treating the negative and cognitive symptoms of schizophrenia (Murphy, Chung et al. 2006; Tandon, Nasrallah et al. 2010). Moreover, antipsychotic medications have been shown to have deleterious effects for both negative and cognitive symptoms in a dose-dependent manner (de Haan, Lavalaye et al. 2004; Artaloytia, Arango et al. 2006; Saeedi, Remington et al. 2006). Additional pharmacologic
strategies to treat negative and cognitive symptoms in schizophrenia remain the focus of ongoing research, although conclusive evidence of benefit to date from such approaches, including antidepressant medications, glycine, and glutamatergic agents, remains elusive (Murphy, Chung et al. 2006; Buchanan 2007; Harvey 2009; Tandon, Nasrallah et al. 2010).

Beyond pharmacologic strategies for the treatment of schizophrenia, there have been numerous psychosocial interventions that have been investigated as adjunctive treatments. This has included individual and family psychoeducational interventions, cognitive behavioural therapy for psychosis, and social skills training, that have shown benefit for the reduction of relapse and rehospitalization rates, reduction in the severity of psychotic symptoms, and improvement in social and community functioning (Tandon, Nasrallah et al. 2010). Cognitive remediation strategies have also been developed to address the cognitive deficits seen in schizophrenia, although this research demonstrates small to moderate effects on cognitive outcomes (Wykes, Huddy et al. 2011). Additionally, cognitive behavioural therapy has been adapted for the treatment of negative symptoms in schizophrenia. Early findings suggested some potential benefit for patients, although overall the limited number of studies have not revealed a consistent benefit to this approach (Rector, Seeman et al. 2003; Klingberg, Wolwer et al. 2011; Jones, Hacker et al. 2012).

1.4 Course and Outcomes

Systematic evaluations of longitudinal outcomes in schizophrenia date back to the work of Kraepelin who highlighted the chronic impairment experienced by individuals with this illness, and noted that adequate recovery occurred in approximately 13% of patients (Kraepelin 1919). Over the ensuing century there have been numerous long-term follow-up studies that have
provided valuable insights into the outcomes of individuals with schizophrenia. While outcomes varied, these studies highlighted the heterogeneity in the course of schizophrenia across individuals, although with the majority experiencing poor long-term outcomes both from symptomatic and functional perspectives, with only the minority (approximately 20% overall) experiencing more favourable outcomes (McGlashan 1988; Jobe and Harrow 2005; American Psychiatric Association 2013). Recognizing this heterogeneity, there have been attempts to delineate distinct course types in schizophrenia. This has resulted in descriptions of up to 73 different mono- and polyphasic course types, with differences mainly driven by the number of psychotic exacerbations as well as degree of inter-episode symptomatic and functional impairment (Huber, Gross et al. 1980; an der Heiden and Hafner 2000). Through this work, what has emerged is the recognition that psychotic symptoms generally become less severe over time, with negative symptoms becoming a more prominent part of the clinical picture over the long-term, and cognitive symptoms remaining relatively stable over the course of the illness (Tandon, Nasrallah et al. 2009).

1.5 Negative Symptoms in Schizophrenia

Recognition of negative symptoms in schizophrenia extends back over a century, with the early work by Kraepelin describing “a weakening of those emotional activities which permanently form the mainsprings of volition …” as the central feature of this illness (Kraepelin 1919). Bleuler was no less sensitive to this issue, noting that “indifference seems to be the external sign of their state…The will …disturbed in a number of ways, but above all by the breakdown of the emotions … The patients appear lazy and negligent because they no longer have the urge to do anything either of their own initiative or at the bidding of another.” (Bleuler 1950).
The assimilation of these symptoms into the construct of “negative symptoms” has its origins in the work of John Russell Reynolds in epilepsy, who initially proposed this terminology to reflect a cluster of symptoms characterized by the loss of “vital properties”, in contrast to “positive symptoms” which he posited were a reflection of an excess of “vital properties”, with these two symptom constructs being independent of each other (Berrios 1985; Pearce 2004; Messinger, Tremeau et al. 2011). It was John Hughlings Jackson who brought this concept forward in psychiatry, building on Reynolds, as well as Spencer’s work on dissolution and evolution of the nervous system, and proposed that negative symptoms reflected a loss of normal function and dissolution of “neural arrangements”, while positive (i.e., psychotic) symptoms represented excess activity that resulted from the loss of higher inhibitory controls and consequent release of lower systems (Jackson 1958; Berrios 1985). In contrast to Reynolds, Jackson viewed these symptoms as closely interrelated, with the negative symptoms reflecting the core lesion of the disease and positive symptoms being a secondary consequence due to loss of top-down inhibitory activity (Berrios 1985).

The introduction of modern psychopharmacology for schizophrenia in the 1950s drove the field’s focus towards assessment and treatment of psychotic symptoms over the ensuing decades. However, there continued to be recognition of the importance of these negative symptoms, driven in large part by the work of John Wing and colleagues throughout the 1960’s and 1970’s (Wing 1989). In the mid-1970’s and early 1980’s formal definitions of positive and negative symptoms emerged, along with subtypes of schizophrenia, and poor-outcome trajectories (Strauss, Carpenter et al. 1974; Crow 1980; Andreasen and Olsen 1982). There also emerged a broader understanding of the negative symptom construct, with definitions including symptoms of affective flattening, alogia, avolition and apathy, anhedonia, and asociality (Andreasen 1982). In addition, a distinction between primary, or idiopathic, and secondary negative symptoms was
highlighted, the latter including iatrogenic, environmental, and disease-related phenomena (e.g., extrapyramidal symptoms, chronic institutionalization, depression, suspicious withdrawal, etc.). A subgroup of individuals with schizophrenia that exhibited primary enduring negative symptoms, even during times of clinical stability, was identified and classified as the “deficit syndrome” (Carpenter, Heinrichs et al. 1988). This classification was found to be stable over many years (Amador, Kirkpatrick et al. 1999; Strauss, Harrow et al. 2010), prevalent in both first-episode and chronic populations (15% and 25-30%, respectively) (Kirkpatrick, Buchanan et al. 2001), and linked to worse long-term outcomes (Strauss, Harrow et al. 2010).

1.5.1 Definition
The emergence of the National Institute of Mental Health (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative on negative symptoms underscores the importance of these symptoms, their impact on outcomes in schizophrenia, and the unmet need that continues to exist for effective treatments of these symptoms (Kirkpatrick, Fenton et al. 2006; Marder, Daniel et al. 2011). While definitions of the symptoms that comprise this symptom domain have varied over the past several decades (Fenton and McGlashan 1992), the emerging consensus from the NIMH negative symptom initiative has identified this domain as consisting of affective flattening, alogia, avolition, asociality, and anhedonia (Kirkpatrick, Fenton et al. 2006).

This consensus definition overlaps extensively with the long-standing definition of negative symptoms proposed by Andreasen (Andreasen 1982). There are, however, some notable differences. Attentional impairment, long considered a negative symptom and a separate subscale of the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982), has
been consistently shown in recent factor analyses to overlap more closely with the disorganized symptom domain in schizophrenia (Peralta and Cuesta 1995; Peralta and Cuesta 1999). Similarly, these studies have also highlighted that symptoms of inappropriate affect and poverty of content of speech, included in the SANS, are also more in line with disorganized rather than negative symptoms (Miller, Arndt et al. 1993; Peralta and Cuesta 1995; Sayers, Curran et al. 1996; Peralta and Cuesta 1999). Consequently, these specific symptoms are typically excluded from investigations of negative symptoms in schizophrenia, as well as from the recent NIMH consensus definition of negative symptoms (Milev, Ho et al. 2005; Blanchard and Cohen 2006; Kirkpatrick, Fenton et al. 2006; Sergi, Rassovsky et al. 2007).

1.5.2 Assessment strategies
In concert with descriptions of negative symptoms in the schizophrenia literature, there have also emerged numerous instruments for evaluating these symptoms. Of the instruments available at the time, the NIMH MATRICS negative symptom initiative consensus statement identified the SANS as the most important rating instrument for assessing these symptoms, one that provides the most extensive coverage of all the negative symptoms (Andreasen 1982; Kirkpatrick, Fenton et al. 2006). Other rating instruments commonly used in outcome and pharmacologic studies in schizophrenia include the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein et al. 1987) and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), which show varying degrees of overlap with the SANS, and although exhibiting good overall inter-correlation, also exclude critical negative symptoms (Fenton and McGlashan 1992; Ernst and Kring 1997). An important and widely implemented instrument designed specifically for the evaluation and diagnosis of primary negative symptoms in the deficit syndrome is the Schedule
for the Deficit Syndrome (SDS), which assesses six key symptoms: restricted affect; diminished emotional range; poverty of speech; curbing of interests; diminished sense of purpose; and, diminished social drive (Kirkpatrick, Buchanan et al. 1989). Another rating instrument that has been used somewhat less frequently is the Negative Symptom Assessment – 16 (NSA-16) (Alphs, Summerfelt et al. 1989), as well as a recent abbreviated 4-item version, the NSA-4 (Alphs, Morlock et al. 2011). Other rating instruments have also been developed over the past decades, including Lewine’s Negative Symptom Scale (Lewine, Fogg et al. 1983), the Negative Symptom Scale by Pogue-Geile and Harrow (Pogue-Geile and Harrow 1985), the Emotional Blunting Scale (Abrams and Taylor 1978), the Manchester Scale (Krawiecka, Goldberg et al. 1977), and the World Health Organization Psychological Impairments Rating Schedule (WHO/PIRS) (Biehl, Maurer et al. 1989), although these did not become as widely used.

From the NIMH MATRICS initiative on negative symptoms, two “next-generation” rating instruments for negative symptoms have emerged - the Brief Negative Symptom Scale (BNSS) (Kirkpatrick, Strauss et al. 2011; Strauss, Hong et al. 2012), and the Clinical Assessment Interview for Negative Symptoms (CAINS) (Horan, Kring et al. 2011; Kring, Gur et al. 2013). Both the BNSS and the CAINS evaluate the 5 core negative symptoms outlined in the NIMH MATRICS consensus definition, although in somewhat different ways. The structure of the 13-item BNSS aligns with the core consensus negative symptoms, although extends previous assessments by evaluating components of anticipatory pleasure and frequency of pleasurable activities, as well as distinguishing between internal experiences and behavior for avolition and asociality (Kirkpatrick, Strauss et al. 2011). The CAINS, also a 13-item scale, is organized along 3 life domains (social, vocational, and recreational), within which motivation, frequency of pleasurable experiences, and anticipation of pleasure are evaluated, followed by an expression
subscale that evaluates vocal prosody, gestures, speech, and facial expression (Kring, Gur et al. 2013).

1.5.3 The case for two distinct subdomains

Negative symptoms are typically described as either a unitary construct or, alternatively, as discrete symptoms of affective flattening or blunting, alogia, asociality, anhedonia, and avolition. Investigations over the past few decades, however, have found that negative symptoms routinely cohere into two separate, yet inter-related, subdomains (Foussias and Remington 2010; Messinger, Tremeau et al. 2011). These studies have relied on factor and component analyses, often using the SANS, largely due to its more extensive coverage of negative symptoms, in individuals with schizophrenia. Consistent with this, the limited investigations using other negative symptom rating scales have found similar symptom clusters.

An evaluation of the factor structure of negative symptoms using the SANS in patients with schizophrenia by Keefe and colleagues (1992) revealed a three-factor structure consisting of: 1) diminished expression, 2) social dysfunction, and 3) disorganization (Keefe, Harvey et al. 1992). Mueser et al. (1994), again using the SANS, identified the same three factors: 1) affective flattening, 2) avolition/apathy and anhedonia/asociality; and 3) alogia and inattention (Mueser, Sayers et al. 1994). Importantly, poverty of speech loaded on the affective flattening factor, whereas other items from the alogia subscale, including poverty of content of speech, aligned more closely with inattention. A similar investigation by Minas et al. (1994) found two central negative symptom factors: 1) negative signs (consisting of affective flattening and poverty of speech items), and 2) psychosocial dysfunction (consisting of symptoms of avolition/apathy and anhedonia/asociality) (Minas, Klimidis et al. 1994). Sayers and colleagues (1996) used a
modified version of the SANS, with inappropriate affect and poverty of content of speech items excluded. Consistent with previous findings, they found a factor structure consisting of: 1) diminished expression (affective flattening); 2) social amotivation (avolition/apathy and anhedonia/asociality); and 3) inattention/alogia (Sayers, Curran et al. 1996). A subsequent investigation by Peralta and Cuesta (1999), using both the SANS and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), identified two subdomains of negative symptoms: 1) poverty of affect and speech (consisting of the affective flattening subscale, except the inappropriate affect item (which loaded on a separate disorganization factor) and poverty of speech and poverty of content of speech items); and 2) social dysfunction (consisting of the avolition/apathy and anhedonia/asociality subscales) (Peralta and Cuesta 1999). In a first-episode psychosis population, Malla and colleagues (2002) also investigated the factor structure of negative symptoms, revealing a two-factor structure for negative symptoms: 1) affective flattening/alogia (except poverty of content of speech), and 2) avolition/anhedonia (Malla, Takhar et al. 2002). In the studies that included both the SAPS and SANS, the attention factor, including poverty of content of speech, and inappropriate affect, routinely loaded with other disorganization symptoms of schizophrenia (Minas, Klimidis et al. 1994; Peralta and Cuesta 1999; Malla, Takhar et al. 2002). Given the important distinction between primary and secondary negative symptoms, and the question of whether the presence of secondary negative symptoms influence the factor structure of negative symptoms, Kelley and colleagues (1999) examined individuals with schizophrenia or schizoaffective disorder both on and off antipsychotic medication. In keeping with earlier findings, they also found a similar two-subdomain structure that remained stable regardless of patient medication status (Kelley, van Kammen et al. 1999).
Outside of studies using the SANS, there have been a few additional factor analyses using other instruments that have explored the underlying factor structure of negative symptoms. Kimhy et al. (2006) investigated the subdomain structure of primary negative symptoms, using the SDS, in individuals with the deficit syndrome and found a similar two-factor structure in primary negative symptoms: 1) avolition (consisting of curbing of interests, diminished sense of purpose, and diminished social drive); and 2) emotional expression (consisting of restricted affect, diminished emotional range, and poverty of speech) (Kimhy, Yale et al. 2006). A recent replication using the SDS by Nakaya and Ohmori (2008) also revealed a two-factor structure consisting of: 1) avolition, and 2) poor emotional expression (Nakaya and Ohmori 2008).

Similarly, initial factor analyses arising from the development of two “next-generation” negative symptom rating instruments, the BNSS and CAINS, have found that items in these rating scales also separate into two discrete factors: 1) diminished expression, and 2) motivation/pleasure (Kirkpatrick, Strauss et al. 2011; Strauss, Hong et al. 2012; Kring, Gur et al. 2013).

Closer inspection of the subdomains of negative symptoms reveals some interesting relationships. In addition to highlighting two subdomains of negative symptoms, these same studies have demonstrated that these two subdomains exhibit a moderate interrelationship (interfactor correlation coefficients between 0.47 and 0.57) (Mueser, Sayers et al. 1994; Sayers, Curran et al. 1996; Peralta and Cuesta 1999). An examination of the separate subscales of the SANS also noted moderate interrelationships for affective flattening with avolition-apathy and anhedonia-asociality subscales ($r=0.49$ and $0.48$, respectively), as well as for alogia with avolition-apathy and anhedonia-asociality subscales ($r=0.61$ and $0.53$, respectively) (Peralta and Cuesta 1995). These findings suggest that the negative symptoms domains and symptoms that comprise them, although distinct phenomenological entities, may reflect a common underlying process.
Overall, contemporary conceptualizations of negative symptoms in schizophrenia align closely with historical notions of these symptoms, although with some important revisions. Symptoms of poverty of content of speech, inappropriate affect, and impairment in attention are now seen to relate more with disorganization symptoms in schizophrenia, rather than with negative symptoms. Further, two discrete, yet related, negative symptom subdomains have emerged – diminished expression (i.e., affective flattening and poverty of speech), and amotivation (i.e., avolition, apathy, asociality, and hedonic deficits). (Figure 1-1)

Figure 1-1. The current conceptualization of negative symptoms in schizophrenia.

1.5.4 Further refinements of the negative symptom construct
Beyond the exploration of the underlying factor structure of negative symptoms, there has also emerged a growing interest in the role of each of these symptoms in schizophrenia. Much of this
work has focused on the symptoms of anhedonia and amotivation in schizophrenia, which are explored below in turn. Of note, the terms avolition, apathy, amotivation, and motivational deficits are viewed as interchangeable within the literature, and thus we have opted for the terms amotivation or motivational deficits in our ensuing discussion of this negative symptom.

Anhedonia, the diminished capacity to experience pleasant emotions (Kring and Germans 2000), or alternatively, difficulty in experiencing interest or pleasure (Andreasen 1982), has long been held to be a core negative symptom in schizophrenia. This has its origins in the work of Chapman and Chapman, where individuals with schizophrenia self-reported increased levels of anhedonia in studies using the Chapman Physical Anhedonia Scale (PAS) and Social Anhedonia Scale (SAS) (Horan, Kring et al. 2006). Inconsistent findings when other rating scales have been used in this population (Loas, Boyer et al. 1996; Horan, Kring et al. 2006), however, along with investigations of the construct and discriminant validity of the PAS and SAS, raise uncertainty regarding the nature of hedonic capacity in schizophrenia (Peterson and Knudson 1983; Leak 1991; Germans and Kring 2000; Leventhal, Chasson et al. 2006). Some recent work examining two discrete components of hedonic experience, anticipatory pleasure (i.e., pleasure derived from anticipating that an activity will be enjoyable) and consummatory pleasure (i.e., pleasure derived from engaging in an enjoyable activity), have yielded mixed results, with Gard and colleagues (2007) finding intact consummatory pleasure but deficits in anticipatory pleasure in schizophrenia subjects compared to healthy controls, although Strauss and colleagues (2011) report the opposite (Gard, Kring et al. 2007; Strauss, Wilbur et al. 2011).

Moving beyond subjective rating instruments for hedonic experience, there have also emerged a series of evaluations using objective experimental paradigms employing emotion-eliciting stimuli ranging from films and pictures to sounds and tastes. These studies have almost
consistently demonstrated that individuals with schizophrenia experience pleasant and unpleasant emotions in the moment with equal intensity when compared to healthy individuals (Berenbaum and Oltmanns 1992; Kring, Kerr et al. 1993; Burbridge and Barch 2007; Heerey and Gold 2007). Importantly, this has been shown to be independent of their diminished emotional expression, as well as medication status. A comparable investigation in individuals meeting criteria for the deficit syndrome also revealed intact in-the-moment hedonic experience in this population when compared to non-deficit schizophrenia and healthy control populations (Earnst and Kring 1999). Notably, Burbridge and Barch (2007) compared self-reported anhedonia using the PAS and SAS with in-the-moment ratings of hedonic experience, using a variety of emotional stimuli, and failed to find a relationship between PAS or SAS ratings and the in-the-moment hedonic ratings (Burbridge and Barch 2007). Further, an investigation in first-episode and chronic schizophrenia patients examining physiological responsiveness to pleasant and unpleasant images also demonstrated intact objective experience of emotions in both groups (Yee, Mathis et al. 2010). Recent systematic reviews of hedonic experience in schizophrenia have come to similar conclusions, suggesting that despite some contradictory findings in the literature the majority of evidence points towards preserved hedonic capacity in this population (Kring and Moran 2008; Cohen and Minor 2010; Llerena, Strauss et al. 2012). In an attempt to reconcile the contradictory findings between subjective and objective ratings of hedonic experience, Strauss and Gold (2012) conclude that reports of diminished hedonic experience derived from self-report ratings scales were related to the use of instruments that evaluated non-current feelings (e.g., feelings related to past or hypothetical experiences) (Strauss and Gold 2012). Based on these findings, it has been suggested that the term “anhedonia” may no longer be an appropriate term in schizophrenia, with more representative terms revolving around “reduced pleasure-seeking behavior” and “beliefs of low pleasure” (Strauss and Gold 2012).
In addition to the improved understanding of emotional experiences, there has also been a renewed focus on motivational deficits in schizophrenia. The early descriptions of the phenomenology of schizophrenia highlighted the central role of volitional disturbances in this illness, which later became incorporated into classifications of negative symptoms and the deficit syndrome (Kraepelin 1919; Bleuler 1950; Andreasen 1982; Carpenter, Heinrichs et al. 1988). Beyond the elevated levels of amotivation found using traditional schizophrenia psychopathology rating instruments, evaluations of motivation using the Apathy Evaluation Scale (AES) (Marin, Biedrzycki et al. 1991) have reaffirmed the presence of motivational deficits in both first-episode and chronic schizophrenia populations (Kiang, Christensen et al. 2003; Faerden, Friis et al. 2009).

There have also been a growing number of investigations focused on discrete components of motivation in schizophrenia. From these, it has been shown that schizophrenia is characterized by impairments in learning about the rewarding properties of stimuli, in addition to coupling behavior to the motivational properties of stimuli, this despite equivalent subjective emotional experiences to these stimuli and independent of medication status (i.e., on or off antipsychotics) (Heerey and Gold 2007; Murray, Clark et al. 2008). Moreover, individuals with schizophrenia have been found to exhibit impairments in anticipating rewards, integrating information about rewards and punishments, maintaining and updating internal value representations, and using this information to guide goal-directed behavior (Juckel, Schlagenauf et al. 2006; Gold, Waltz et al. 2008; Murray, Clark et al. 2008; Barch and Dowd 2010; Nielsen, Rostrup et al. 2012). Individuals with schizophrenia have also been shown to more rapidly discount the value of larger future rewards in favor of smaller more immediate rewards (Heerey, Robinson et al. 2007; Ahn, Rass et al. 2011). In contrast to these impairments in motivation that are often evident in the context of external rewards, investigations of intrinsic motivation in schizophrenia have yielded
mixed results, with some findings suggesting intact intrinsic motivation (Barch, Yodkovik et al. 2008), while others report impairment in this facet of motivation (Choi and Medalia 2010). Interestingly, recent work examining negative symptoms from a cognitive perspective have identified dysfunctional attitudes, and specifically defeatist performance beliefs, as an important psychological factor linked to negative symptoms, and more specifically motivational deficits, in schizophrenia (Rector, Beck et al. 2005; Grant and Beck 2009; Horan, Rassovsky et al. 2010).

1.5.5 A separate domain of psychopathology
The negative symptoms in schizophrenia have long been recognized as a discrete domain of psychopathology, separate from both positive and disorganized symptoms. Factor analyses over the past thirty years have repeatedly demonstrated that negative symptoms constitute a separate domain from both positive symptoms and disorganization in both chronic and first-episode populations (McGlashan and Fenton 1992; Andreasen, Arndt et al. 1995; Marder, Davis et al. 1997; White, Harvey et al. 1997; Drake, Dunn et al. 2003; Emsley, Rabinowitz et al. 2003; Kopelowicz, Ventura et al. 2008; Tandon, Nasrallah et al. 2009; Wallwork, Fortgang et al. 2012). There has been uncertainty, however, around the relationship between negative symptoms and depression, as well as cognitive impairment seen in schizophrenia.

1.5.5.1 Relationship with depression
Factor analyses involving traditional psychopathology ratings scales, including the Brief Psychiatric Rating Scale (Overall and Gorham 1962) and the Positive and Negative Syndrome Scale (Kay, Fiszbein et al. 1987) have shown that in both first-episode and chronic schizophrenia
patients negative symptoms comprise a separate symptom domain from depressive symptoms (Marder, Davis et al. 1997; White, Harvey et al. 1997; Ventura, Nuechterlein et al. 2000; Emsley, Rabinowitz et al. 2003; Kopelowicz, Ventura et al. 2008; Wallwork, Fortgang et al. 2012). Cross-sectional and longitudinal examinations of the relationship between negative symptoms and depression have also found that these two domains exhibit, at most, modest and inconsistent overlap (Lewine 1990; Addington, Addington et al. 1994; Addington, Addington et al. 1996; Collins, Remington et al. 1996; Herbener and Harrow 2001; Kirkpatrick, Strauss et al. 2011; Kring, Gur et al. 2013). This has also included examination of individuals both on and off antipsychotic medications (Lewine 1990). The inconsistency in findings across different studies, however, appears to be driven by the type of depression severity instrument used, as well as the clinical stability of the patients evaluated (Addington, Addington et al. 1994; Addington, Addington et al. 1996; Collins, Remington et al. 1996). Overall, these findings suggest that negative symptoms and depression exist as essentially distinct domains of psychopathology in schizophrenia, and any overlap between them appears to be modest.

1.5.5.2 Relationship with cognitive deficits

Neurocognitive deficits across multiple domains have been repeatedly identified in schizophrenia including: verbal and non-verbal memory; working memory; motor speed; attention/vigilance; general intelligence; visuospatial ability; processing speed; verbal fluency; executive function; and language (Heinrichs and Zakzanis 1998; Kern, Green et al. 2004). In cross-sectional studies, neurocognitive deficits have frequently shown significant relationships with negative symptoms, raising questions as to the nature of their relationship and whether they represent one and the same area of psychopathology, merely measured differently. Efforts to clarify this have revealed
that several domains of neurocognitive function show a low-to-moderate inverse relationship with negative symptoms, although with no specific neurocognitive deficit standing out as driving this relationship (reviewed in (Addington 2000; Harvey, Koren et al. 2006)). Moreover, the degree of overlap between these two symptom domains in schizophrenia has been estimated to be small (Addington 2000). An extensive evaluation of this relationship by Harvey and colleagues (2006) suggested that negative symptoms and neurocognitive dysfunction appear to be related, but separate, domains of psychopathology, with the observed relationship possibly influenced by their shared relationship with other features of schizophrenia, such as functional outcomes (Harvey, Koren et al. 2006). In addition, an investigation of the course of negative and neurocognitive symptoms in schizophrenia failed to find a longitudinal relationship between these symptom domains, consistent with previous conclusions that negative symptoms and neurocognition represent separate psychopathological domains (Bell and Mishara 2006). A subsequent longitudinal examination of the relationship between motivational deficits and neurocognition revealed similar findings, with these two domains changing independently over time (Nakagami, Hoe et al. 2010).

There has been, however, growing recognition of the potential impact of motivation on cognitive test performance, with questions as to whether some of the cognitive impairment seen in schizophrenia is driven by a lack of motivation to do well on cognitive tasks (Barch 2005). Early work by Schmand et al. (1994) explored this question within a computational-energetic framework, with the view that computational mechanisms relate to the information processing necessary to carry out cognitive tasks, while energetic mechanisms relate to energizing or motivational aspects of information processing such as arousal and mental effort (Schmand, Kuipers et al. 1994). In their investigation examining performance of psychotic and non-psychotic disorder psychiatric patients on a simple reaction task they found that the psychotic
group exhibited energetic deficits, but without computational impairment, and further, that those with energetic deficits performed significantly worse on attention, vigilance, and verbal memory tasks. Based on their findings, they suggested that cognitive dysfunction in psychotic disorders was related more to deficits in energetic (i.e., motivation) rather than computational mechanisms (Schmand, Kuipers et al. 1994). In keeping with this, motivational deficits measured clinically have shown significant relationships with cognitive performance, and specifically with verbal fluency, working memory, attention and set-shifting, and verbal learning and memory (Addington and Addington 1999; Roth, Flashman et al. 2004; Nakagami, Xie et al. 2008; Faerdin, Vaskinn et al. 2009; Gard, Fisher et al. 2009; Konstantakopoulos, Ploumpidis et al. 2011). Further, evaluations of reward- and punishment-driven learning deficits seen in individuals with schizophrenia have been related to the severity of negative symptoms, but not cognitive functioning (Waltz, Frank et al. 2007; Strauss, Frank et al. 2011). In contrast, deficits in coupling behavior to the motivational properties of stimuli were found to be related to working memory impairment in individuals with schizophrenia (Heerey and Gold 2007). Additionally, the rate at which the value of larger future rewards were discounted, compared to smaller more immediate rewards, was found to be inversely correlated with working memory performance in schizophrenia patients (Heerey, Robinson et al. 2007). Finally, use of monetary incentives to evaluate the impact of motivation on cognitive task performance has revealed that on some cognitive tasks, such as the Wisconsin Card Sorting Task (Heaton 1981), the Span of Apprehension (Asarnow and Nuechterlein 1987), and facial emotion recognition tasks (Kerr and Neale 1993), performance can be improved through the use of such incentives (Summerfelt, Alphs et al. 1991; Kern, Green et al. 1995; Penn and Combs 2000). Importantly, this has not been consistent across all studies (Green, Ganzell et al. 1990), highlighting that motivational deficits may differentially impact functioning across cognitive domains.
An alternative approach to investigate the impact of motivational deficits on cognitive test performance has been to assess the degree of effort individuals exert during cognitive testing. This has routinely been accomplished in neuropsychological examinations through the use of performance validity tests (PVTs). Such PVTs often employ forced-choice tasks whereby individuals are presented a series of verbal or visual stimuli, followed by presentation of pairs of stimuli from which they must identify the one that was previously presented (Bianchini, Mathias et al. 2001). PVTs have mostly been employed in the context of litigation and compensation assessments to identify malingering. Their use, however, has not been without controversy, given the absence of a “gold standard” for cognitive effort, and their validation based on simulation or known-group designs, both of which present their own limitations (Bianchini, Mathias et al. 2001; Bigler 2012). Nonetheless, PVTs are seen as an important component of neuropsychological evaluations to evaluate whether participants are providing sufficient effort during neuropsychological testing (Sharland and Gfeller 2007; McCarter, Walton et al. 2009; Fox 2011). Moreover, PVTs have been increasingly used for the assessment of effort in non-litigation settings, including in children, adolescents, healthy undergraduate university student volunteers, and in patients with neurological conditions including epilepsy, Alzheimer’s disease, and traumatic brain injury patients (Merten, Bossink et al. 2007; Locke, Smigielski et al. 2008; Axelrod and Schutte 2011; Kirk, Harris et al. 2011; An, Zakzanis et al. 2012; Brooks, Sherman et al. 2012; Wisdom, Brown et al. 2012).

Across psychiatric populations, investigations using PVTs have revealed that depression and anxiety disorders do not appear to impact PVT scores (reviewed in (Goldberg, Back-Madruga et al. 2007)). In schizophrenia, however, there have been mixed findings. Early studies using PVTs in schizophrenia populations identified 13% to 27% of individuals as exerting insufficient effort (i.e., failing the PVT) (Back, Boone et al. 1996; Goldberg, Back-Madruga et al. 2007).
Ensuing work by Egeland et al. (2003), comparing individuals with schizophrenia, depression, and healthy controls, using the Victoria Symptom Validity Test (VSVT) to assess effort, found that 5% of individuals with schizophrenia exerted insufficient effort, which was not significantly different from other groups where no individuals exerted insufficient effort (Egeland, Sundet et al. 2003). An investigation by Duncan (2005) in individuals with psychotic disorders using the Test of Memory Malingering (TOMM; (Tombaugh 1996)), one of the most frequently used PVTs (Sharland and Gfeller 2007; McCarter, Walton et al. 2009), found that 8% of participants exerted insufficient effort, and that this appeared to be driven by concentration impairments (Duncan 2005).

A subsequent examination by Gorrisen et al. (2005) explored the impact of effort on cognitive test performance in individuals with schizophrenia compared to non-schizophrenia psychiatric controls (including subjects with depression, anxiety, personality disorders, eating disorders, and adjustment disorders), neurological controls (including participants with traumatic brain injury, neurodegenerative disorders, vascular disorders, brain tumors, epilepsy, and multiple sclerosis), as well as healthy control participants (Gorissen, Sanz et al. 2005). In their study, using another common PVT, the Word Memory Test (WMT), they found the prevalence of insufficient effort to be 72% in the schizophrenia group, compared to 25% in the psychiatric control group, 10% in the neurological control group, and 0% in the healthy control group. Effort accounted for between 14% and 35% of the variance in cognitive test scores, and was significantly correlated with negative symptom severity in the schizophrenia group (Gorissen, Sanz et al. 2005).

A more recent study, however, by Avery et al. (2009) also used the WMT to assess effort in schizophrenia participants, and found much better performance in their sample, with average scores on the WMT comparable to the psychiatric control group in Gorrisen et al. (2005) (Avery,
Startup et al. 2009). Interestingly, while effort correlated with total negative symptoms, this appeared to be driven by relationships with alogia and anhedonia, but with no significant relationship with avolition. Finally, Schroeder and Marshall (2011) examined performance across seven PVTs in psychotic and non-psychotic psychiatric populations, and found that insufficient effort determined by failure on a single PVT was equally prevalent in psychotic and non-psychotic groups (19% and 17%, respectively) (Schroeder and Marshall 2011). Using more stringent criteria (i.e., requiring failure on two PVTs) they found reduced, and non-significantly different, prevalence rates of insufficient effort in psychotic and non-psychotic participant groups (7% and 5%, respectively). Of note, in these studies using PVTs insufficient effort was defined as performing below an established cut-off score for the particular instrument(s), rather than scoring in the “chance” range (i.e., 50% correct) which would have been suggestive of specific effort to do poorly on the PVT.

Another strategy to evaluate mental effort employed by Granholm and colleagues (2007) examined pupillary responses during cognitive testing to index mental effort, with greater pupillary dilation being indicative of increased mental effort (Granholm, Verney et al. 2007). In comparison to healthy participants, there existed two groups of schizophrenia participants, one exerting normal mental effort and one exerting reduced mental effort during cognitive testing, with pupillary responses being significantly correlated with negative symptom severity. While individuals in both groups showed equal impairment in cognitive task performance, those in the low effort group had more severe negative symptoms. More recently, work by Gold and colleagues (2013) investigating effort-cost computations in schizophrenia found that willingness to exert effort during a decision-making task was correlated with better global cognitive performance, and in particular with processing speed, verbal and visual memory, and reasoning/problem solving domains (Gold, Strauss et al. 2013).
Social cognition, a specific domain of cognitive functioning that refers to “the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others” (Green, Penn et al. 2008), has also emerged as an important area of psychopathology in schizophrenia (Schmidt, Mueller et al. 2011; Lee, Altshuler et al. 2013). This construct is believed to consist of at least five distinct domains: theory of mind; social perception; social knowledge; attributional bias; and, emotional processing (reviewed in (Green, Penn et al. 2008)). Despite recent advances in our understanding of social cognition deficits in schizophrenia, however, its relationship with other important symptom domains such as neurocognition and negative symptoms remains unclear. Sergi and colleagues (2007) have shed some light on this issue in a recent cross-sectional investigation; through structural equation modeling they found that social cognition and neurocognition are distinct, yet highly related, constructs (Sergi, Rassovsky et al. 2007). In addition, social cognition and negative symptoms, as assessed by the SANS, are also distinct constructs. A proposed three-factor model suggests that the relationship between social cognition and negative symptoms, while significant, is weaker than that between social cognition and neurocognition.

1.5.6 Functional consequences

Schizophrenia is generally considered to be a disorder marked by poor functional outcomes (McGlashan 1988; Jobe and Harrow 2005), and the search for more effective therapeutic options for this disorder has led to countless investigations of the predictors of these poor outcomes. Through these efforts, negative symptom severity has been consistently linked to worse functional outcomes in schizophrenia, including specific relationships with impaired

Similarly, persistent negative symptoms, both primary negative symptoms in the deficit syndrome, as well as persistent negative symptoms more broadly defined, have been linked to worse functional outcomes (Kirkpatrick, Buchanan et al. 2001; Strauss, Harrow et al. 2010; Hovington, Bodnar et al. 2012).

Investigations of discrete subdomains of negative symptoms and functional outcomes in schizophrenia have served to highlight some critical symptoms that may drive these relationships. The amotivation subdomain of negative symptoms has demonstrated a significant relationship to functional outcomes in schizophrenia, including instrumental role performance, household adjustment, extended family functioning, and social/leisure functioning (Sayers, Curran et al. 1996; Green, Hellemann et al. 2012). In line with this, a series of investigations in both first-episode and chronic schizophrenia populations have found motivational deficits to be significantly correlated with functioning, both cross-sectionally (Kiang, Christensen et al. 2003; Nakagami, Xie et al. 2008; Faerden, Friis et al. 2009; Foussias, Mann et al. 2009; Konstantakopoulos, Ploumpidis et al. 2011; Kring, Gur et al. 2013), and longitudinally (Faerden, Finset et al. 2010; Foussias, Mann et al. 2010; Evensen, Rossberg et al. 2012). The relationship between anhedonia and functional outcomes has also received considerable attention although with mixed results. In some short-term and long-term follow-up studies, anhedonia, typically measured with the PAS and SAS, has correlated with functional outcomes (Blanchard, Mueser et al. 1998; Herbener, Harrow et al. 2005), but not in others (Katsanis, Iacono et al. 1992). Further, the relationships between anticipatory/consummatory pleasure and functional outcomes have
been inconsistent, with some suggestion of a link between anticipatory pleasure and functioning in one study (Gard, Kring et al. 2007); however, this was not replicated (Strauss, Wilbur et al. 2011).

Findings regarding a relationship between the diminished expression subdomain of negative symptoms and functional outcomes in schizophrenia have been mixed, with a relationship found in one study (Kring, Gur et al. 2013), but not in others, particularly after accounting for the predictive role of amotivation (Sayers, Curran et al. 1996; Foussias, Mann et al. 2009; Green, Hellemann et al. 2012). In addition, affective flattening has not been found to be related to social skills performance (Salem and Kring 1999). There has been one study, however, where affective flattening was associated with functional outcomes both cross-sectionally and longitudinally, although this is potentially confounded by the concurrent presence of more severe negative symptoms overall in the group with worse affective flattening (Gur, Kohler et al. 2006).

Cognitive dysfunction, including both neurocognition and social cognition, has also been repeatedly found to play a significant role in determining functional outcomes in schizophrenia (Green, Kern et al. 2000; Green, Kern et al. 2004; Schmidt, Mueller et al. 2011), with questions emerging around their possible interactions. Evidence suggests both neurocognition and negative symptoms are significantly related to functional outcomes, although negative symptoms appear to play an additional role in that they at least partially mediate the relationship between neurocognition and functioning (Lipkovich, Deberdt et al. 2009; Ventura, Hellemann et al. 2009; Ojeda, Sanchez et al. 2012). Further explorations of this mediating role of negative symptoms have revealed that motivational deficits appear to be particularly important in explaining the relationship between both neurocognitive and social cognitive dysfunction and functional
outcomes in schizophrenia (Nakagami, Xie et al. 2008; Gard, Fisher et al. 2009; Green, Hellemann et al. 2012). (Figure 1-2)

Figure 1-2. Schematic representation of the role of motivation, and deficits therein, in predicting functional outcomes in schizophrenia.

Motivation exhibits both a direct effect on functional outcomes, as well as playing a mediating role along a path from neurocognition to social cognition to functioning. Social cognition mediates the relationship between neurocognition and functional outcomes, and further has a direct effect on functional outcomes, although part of this is mediated through motivation.
1.6 Negative Symptoms Across the Schizophrenia Spectrum

While most studies have focused on the evaluation of negative symptoms in individuals with schizophrenia, at times with a mixed sample including individuals with schizoaffective disorder, there have also been efforts specifically comparing the nature of negative symptoms between these two diagnostic groups. Through this work, cross-sectional and longitudinal studies have found negative symptoms overall to be more severe in schizophrenia than schizoaffective disorder (Kendler, McGuire et al. 1995; Peralta, Cuesta et al. 1997; Moller, Bottlender et al. 2000; Moller, Bottlender et al. 2002; Jager, Bottlender et al. 2003; Averill, Reas et al. 2004; Bora, Yucel et al. 2009). Several studies, however, have found that only poverty of speech and affective flattening was more severe in schizophrenia versus schizoaffective disorder, with other negative symptoms of equivalent severity between groups (Fennig, Bromet et al. 1996; Pini, de Queiroz et al. 2004). Unfortunately, there are no studies to date that have examined the differential expression of hedonic or motivational deficits between these disorders. In addition, there has been some limited examination of the underlying subdomain structure of negative symptoms in schizoaffective disorder. In heterogeneous samples consisting of individuals with schizophrenia and schizoaffective disorder, factor analyses have revealed a subdomain structure for negative symptoms in keeping with findings in schizophrenia (Sayers, Curran et al. 1996; Peralta, Cuesta et al. 1997; Peralta and Cuesta 1999). While the authors have suggested that this supports a lack of difference in the subdomain structure of negative symptoms between schizophrenia and schizoaffective disorder, more focused investigations directly comparing these two diagnostic groups are necessary before drawing any firm conclusions.

The nature and expression of negative symptoms has also been examined in the prodromal phase of schizophrenia, with prospective investigations relying on assessments of individuals deemed
to be at high risk of developing the illness, i.e., those with an at-risk mental state (Yung and McGorry 1996). Studies in this population have underscored the presence of a discrete negative symptom domain early in the developmental course of schizophrenia, including symptoms of amotivation, diminished emotional expression and experience, decreased ideational richness, and social isolation and withdrawal (Hawkins, McGlashan et al. 2004; Demjaha, Valmaggia et al. 2010). Negative symptoms are, in fact, some of the most frequently reported features observed in the early phase of the prodrome and in advance of psychotic symptoms (Yung and McGorry 1996; an der Heiden and Hafner 2000; Gourzis, Katrivanou et al. 2002; Cornblatt, Lencz et al. 2003). In line with findings in schizophrenia, the severity of these negative symptoms has also been linked to functional impairment in at-risk individuals (Niendam, Bearden et al. 2006; Svirskis, Korkeila et al. 2007; Corcoran, Kimhy et al. 2010; Demjaha, Valmaggia et al. 2010). In addition, a recent evaluation of subjective hedonic experiences to visual stimuli that included physiological responsiveness and arousal measures found that at-risk individuals exhibit patterns of emotional experience similar to healthy control and schizophrenia populations (Yee, Mathis et al. 2010).

Family studies in schizophrenia have identified several personality disorders deemed to be genetically related to schizophrenia (i.e., schizophrenia spectrum disorders, including schizotypal, schizoid, paranoid and, in some studies, avoidant personality disorders) (Kendler and Gardner 1997; Tienari, Wynne et al. 2003; Fogelson, Nuechterlein et al. 2007; Gooding, Tallent et al. 2007). Most studies of this sort however, have focused on schizotypy, either categorically within the formal diagnostic group of schizotypal personality disorder (SPD) or, alternatively, as a dimensional measure of schizotypal traits. This focus has been driven by evidence that schizotypy bears the closest and most consistent genetic relationship with schizophrenia (Kendler 2003; Tienari, Wynne et al. 2003), and may represent an intermediate
schizophrenia phenotype (Meehl 1962). Factor analyses evaluating the dimensions of schizotypy, both categorically and dimensionally, have identified the existence of a negative schizotypy dimension, consisting of symptoms of social withdrawal, anhedonia, poverty of speech, and blunted affect, a profile that bears striking resemblance to the negative symptom domain in schizophrenia (Vollema and van den Bosch 1995; Gruzelier 1996; Siever and Davis 2004; Raine 2006). Investigations of discrete negative symptoms in schizotypy have focused primarily on hedonic deficits, with objective laboratory-based investigations producing mixed findings; some studies have found intact hedonic experience (Berenbaum, Snowhite et al. 1987; Gooding, Davidson et al. 2002), while others have demonstrated some deficits (Ferguson and Katkin 1996). Additionally, an examination of affective expression in this population in the context of laboratory-based emotional stimuli viewing failed to find a difference between schizotypal and healthy control populations (Berenbaum, Snowhite et al. 1987).

1.7 Negative Symptoms Beyond Schizophrenia

While negative symptoms have traditionally been described in the context of schizophrenia and related psychoses, it has become increasingly apparent that these same negative symptoms are present in a host of other neuropsychiatric illnesses. Major depressive disorder (MDD) represents the most commonly considered disorder in which negative symptoms have been described, with findings around the distinction between depression and negative symptoms in schizophrenia described above. In addition, comparisons between schizophrenia and non-schizophrenia populations (affective disorders, neuroses, and personality disorders) have found more frequent and severe negative symptoms in schizophrenia patients (Lewine 1990; Herbener and Harrow 2001), although others have reported equivalent frequencies and severity of negative
symptoms in both groups (Gerbaldo, Helisch et al. 1994; Klosterkotter, Albers et al. 1995). This has included examinations of primary negative symptoms and the deficit syndrome (Gerbaldo, Helisch et al. 1994), leading to the suggestion that, at least when evaluated cross-sectionally, negative symptoms do not serve as a valuable discriminator between schizophrenia and non-schizophrenia disorders (Klosterkotter, Albers et al. 1995). Evaluations of the enduring nature of negative symptoms however, have routinely found that individuals with schizophrenia experience enduring primary negative symptoms more frequently than MDD or other non-schizophrenia patients, with this enduring quality being a more specific predictor of a diagnosis of schizophrenia (Lewine 1990; Gerbaldo, Fickinger et al. 1995; Herbener and Harrow 2001; Bottlender, Sato et al. 2003; Bottlender, Sato et al. 2003). These findings have been shown to be consistent across both acute inpatients at time of admission and patients five years after index admission, free of current depressed mood or psychosis, no longer fulfilling criteria for MDD, and not being treated with antipsychotic medication for at least 12 months. Of note, these same studies report that between 20% and 40% of individuals with MDD also experience enduring negative symptoms, which may represent residual symptoms between episodes (Herbener and Harrow 2001; Bottlender, Sato et al. 2003).

In addition, a factor analysis of all Hamilton Rating Scale for Depression (HRSD) and SANS items in patients with schizophrenia, schizoaffective disorder – depressed type, and MDD revealed that negative and depressive symptoms in these groups loaded on discrete factors, suggesting they are phenomenologically distinct symptom clusters (Kitamura and Suga 1991). Similarly, an examination of two discrete components of the HRSD in patients with MDD, a depressive symptoms factor (HRSD-DS) and a negative symptom factor (HRSD-NS: consisting of items related to involvement in work/activities, psychomotor retardation, and energy level), found that while the HRSD-NS correlated with the SANS and PANSS negative subscale scores,
this was not the case for the HRSD-DS (Galynker, Cohen et al. 2000). Further, the HRSD-DS was highly correlated with the HRSD total score, whereas the HRSD-NS was not. In addition, there has been some suggestion that the melancholic subtype of MDD shares the closest relationship with negative symptoms as seen in schizophrenia (Bermanzohn and Siris 1992; Winograd-Gurvich, Fitzgerald et al. 2006).

Negative symptoms have also been increasingly recognized in other neuropsychiatric illnesses, and described variably as either negative symptoms or apathy. Specifically, negative symptoms have been frequently identified in individuals with Parkinson’s disease (PD), Alzheimer’s disease (AD), Huntington’s disease (HD), Frontotemporal Dementia, Progressive Supranuclear Palsy, Temporal Lobe Epilepsy (TLE), Multiple Sclerosis, and Traumatic Brain Injury (TBI) (Marin, Biedrzycki et al. 1991; Levy, Cummings et al. 1998; Brown and Pluck 2000; Pluck and Brown 2002; Geary, Seidenberg et al. 2009). In PD, in addition to the characteristic affective flattening that characterizes this illness, there has been a consistent recognition of the presence of apathy, with prevalence rates between 17% and 70% (Brown and Pluck 2000; Aarsland, Marsh et al. 2009). Some studies in this population have documented a relationship between apathy and depression (Levy, Cummings et al. 1998; Starkstein, Merello et al. 2009), although many have not found this relationship (Brown and Pluck 2000; Pluck and Brown 2002; Kirsch-Darrow, Fernandez et al. 2006). Further, even in those studies where depression was related to apathy, there continued to be individuals with PD who exhibited symptoms of apathy in the absence of any depressive symptoms (Brown and Pluck 2000; Aarsland, Marsh et al. 2009; Starkstein, Merello et al. 2009).

Investigations in AD have also highlighted the presence of negative symptoms, with prevalence rates of apathy from 30% to 92%, increasing with dementia severity (Reichman, Coyne et al.
1996; Brown and Pluck 2000; Vercelletto, Martinez et al. 2002; Clarke, van Reekum et al. 2008). In addition, an investigation using a modified SANS for this population (SANS-AD) found that individuals with AD exhibit significantly more severe negative symptoms compared to healthy elderly controls in the absence of any significant difference in depression severity between the two groups, with this difference, in large part, a product of more severe apathy and social-emotional withdrawal (Reichman, Coyne et al. 1996). In line with this, others have found negative symptoms in AD to represent a separate symptom domain from depression (Levy, Cummings et al. 1998; de Jonghe, Goedhart et al. 2003), although not all (Starkstein, Jorge et al. 2006). In individuals with HD, apathy has also been described, with a prevalence of 59% (Levy, Cummings et al. 1998). Importantly, this has been observed in individuals both with and without depression, and with severity of apathy unrelated to depression severity.

Negative symptoms have also been demonstrated to occur in 31% of individuals with temporal lobe epilepsy; affective flattening, alogia, anhedonia, and apathy have all been reported with a high frequency (Getz, Hermann et al. 2002). Importantly, depression was unrelated to negative symptoms in this population. Finally, apathy has been recognized as a frequent neuropsychiatric sequela of TBI, with prevalence rates between 42% and 46% (Andersson, Krogstad et al. 1999; Ciurli, Formisano et al. 2011). In comparison with schizophrenia patients meeting DS criteria, TBI patients exhibited equivalent apathy severity, while DS patients experienced more severe affective flattening, alogia, and anhedonia (Rao, Spiro et al. 2007).

Moving beyond phenomenological characterization of negative symptoms, the relationship between these symptoms and functional outcomes has been explored across at least some of the neuropsychiatric illnesses highlighted above. In MDD, patients exhibiting severe negative symptoms have been found to show less improvement over the course of treatment, and to have
more concurrent and longitudinal deficits in adaptive functioning, including social and work functioning, as well as higher rehospitalization rates. (Chaturvedi and Sarmukkaddam 1986; Chaturvedi and Sarmukkaddam 1986; Herbener and Harrow 2004) Studies examining the correlates of functional outcomes in AD have also found negative symptoms to contribute to functional deficits, with apathy specifically being related to greater functional decline, including basic self-care and instrumental activities of daily living deficits. (Doody, Massman et al. 1995; Starkstein, Jorge et al. 2006; Clarke, van Reekum et al. 2008) Similarly, the avolition-apathy subscale of the SANS-AD strongly correlated with functional competence in activities of daily living. (Reichman and Negron 2001) Consistent with findings in other neuropsychiatric illnesses, the presence of negative symptoms in patients with TLE has been found to portend higher psychosocial disability, including dependence on social assistance, lower marital/cohabitation rates, and lower quality of life (including more social isolation, impairment in work, driving, and social functioning). (Getz, Hermann et al. 2003)

1.8 Neurobiological Underpinnings of Negative Symptoms in Schizophrenia

Along with their phenomenological descriptions of schizophrenia and their emphasis on the centrality of negative symptoms, Kraepelin and Bleuler, building on emerging evidence by Alzheimer of neuronal loss in the frontal cortex of the brains of individuals with schizophrenia, also speculated that these symptoms arose from structural and functional abnormalities in the frontal lobes of the brain (Alzheimer 1913; Kraepelin 1919; Bleuler 1950). Early interest in these symptoms and their neurobiological underpinnings however, faded due to multiple factors including the lack of available investigative techniques and the shifting focus in the field towards
positive symptoms, their neurobiology, and treatment. With growing recognition of the importance of negative symptoms in the course and outcome of schizophrenia, as well as advances in neuroimaging techniques, there has been a growing body of literature exploring the structural and functional brain correlates of negative symptoms as well as brain regions that may be critical in the development of specific negative symptoms. Below this expanding field of research in schizophrenia is reviewed, as well as investigations pertaining to the other schizophrenia spectrum illnesses where available. Of note, the majority of neurobiological investigations have included samples consisting primarily of individuals with schizophrenia, although often individuals with schizoaffective disorder have also been included. To date, there do not appear to be studies that have examined differential structural and functional brain correlates of negative symptoms between schizophrenia and schizoaffective disorder. In the sections that follow findings in schizophrenia are discussed, although it is acknowledged that these are often results from mixed samples.

1.8.1 Structural and functional imaging studies

Investigations of the structural brain correlates of negative symptoms, involving computed tomography (CT) and magnetic resonance imaging (MRI) studies, have offered mixed results. Early work in this field by Andreasen et al. (Andreasen, Nasrallah et al. 1986) demonstrated reductions in frontal lobe volumes in schizophrenia, but failed to demonstrate a relationship with negative symptom severity. A subsequent study by the same group found that patients with prominent negative symptoms had significantly enlarged cerebral ventricles compared to patients with mixed or prominent positive symptomatology (Andreasen, Swayze et al. 1990). Other structural imaging studies examining frontal lobe volume changes have collectively shown only
modest differences in frontal lobe volumes between patients with schizophrenia and healthy controls (Zakzanis and Heinrichs 1999), and most investigations have failed to demonstrate a specific relationship between total frontal lobe volume and negative symptoms (Baare, Hulshoff Pol et al. 1999).

More detailed examinations of specific brain regions, rather than total regional volumes, have documented some important associations with negative symptoms. Several studies have revealed significant associations between negative symptom severity and reduction in prefrontal cortical (PFC) volumes, including orbitofrontal (OFC), medial and lateral prefrontal cortices (Baare, Hulshoff Pol et al. 1999; Sanfilipo, Lafargue et al. 2000; Wible, Anderson et al. 2001; Hazlett, Buchsbaum et al. 2008; Koutsouleris, Gaser et al. 2008). In addition, volumetric studies have also revealed associations between negative symptoms and volume reductions in temporal cortex (Hazlett, Buchsbaum et al. 2008; Koutsouleris, Gaser et al. 2008), bilateral caudate (Young, Blackwood et al. 1991), limbic (Koutsouleris, Gaser et al. 2008), right parietal cortex (Zetzsche, Preuss et al. 2008), left fusiform gyrus (Nestor, Onitsuka et al. 2007), and corpus callosum (Tibbo, Nopoulos et al. 1998). There have also been contradictory findings, however, including associations between negative symptom severity and increased volume including cortical and frontal gray matter (Nesvag, Saetre et al. 2009), OFC (Lacerda, Hardan et al. 2007), right posterior superior temporal gyrus (Kim, Crespo-Facorro et al. 2003), and hippocampus (Szendi, Kiss et al. 2006).

Advances in MRI resolution and processing techniques have also enabled investigators to evaluate the integrity of white matter tracts in the brain, a modality entitled diffusion tensor imaging (DTI). Studies using this imaging modality have demonstrated an association between negative symptom severity and abnormalities in orbitofrontal white matter tract integrity.
(Wolkin, Choi et al. 2003), internal capsule and superior longitudinal fasciculus, corpus callosum, anterior thalamic radiations, fronto-occipital fasciculus, left temporal lobe white matter tracts (Mitelman, Torosjan et al. 2007), and bilateral uncinate fasciculi (Szeszko, Robinson et al. 2008). These findings, however, have not been consistent between studies (Skelly, Calhoun et al. 2008; Szeszko, Robinson et al. 2008).

Longitudinal investigations examining progressive structural brain changes and their associations with symptomatology have also offered valuable insights. A recent systematic review of the longitudinal structural imaging literature in schizophrenia revealed that there is consistent evidence for progressive reductions in overall brain tissue volume and enlargement in lateral ventricle volumes, with changes being most pronounced in frontal and temporal cortices (Hulshoff Pol and Kahn 2008). In addition, several groups have demonstrated associations between negative symptom severity and progressive volume reductions in frontal lobe (Ho, Andreasen et al. 2003), prefrontal and posterior temporal lobe (Mathalon, Sullivan et al. 2001), and left insular cortex (Takahashi, Wood et al. 2009). There have also been studies that have found inverse associations (i.e., an association between improvement in negative symptoms over time and progressive brain volume decreases), as well as other studies failing to find an association (reviewed in (Hulshoff Pol and Kahn 2008)).

Additional investigations aimed at evaluating structural pathology in schizophrenia have utilized proton magnetic resonance spectroscopy to evaluate concentrations of the intraneuronal chemical N-acetylaspartate (NAA), with reduced NAA concentrations being indicative of a higher degree of neuronal pathology. Some of these studies have demonstrated a significant relationship between reduced prefrontal NAA concentration and more severe negative symptoms (Callicott,
Bertolino et al. 2000; Tanaka, Obata et al. 2006). Others however, have failed to replicate this association (Sigmundsson, Maier et al. 2003).

In keeping with the large number of structural imaging studies that have been conducted over the past several decades, there has been an accumulation of imaging studies that have examined the functional brain correlates of negative symptoms in schizophrenia using a variety of techniques including single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI (fMRI). Examinations of cerebral metabolism in individuals with schizophrenia have demonstrated a relationship between negative symptom severity and reduced frontal metabolism (Volkow, Wolf et al. 1987; Schroder, Buchsbaum et al. 1996), particularly in the dorsolateral prefrontal cortex (DLPFC) (Wolkin, Sanfilipo et al. 1992) and ventral prefrontal and temporal cortices (Potkin, Alva et al. 2002). Others, though, have failed to find a significant association between negative symptom severity and hypometabolism (Siegel, Buchsbaum et al. 1993). In addition, evaluations of regional cerebral blood flow (rCBF) have demonstrated an association between more severe negative symptoms and reduced rCBF in frontal, DLPFC, cingulate, temporal, basal ganglia, and thalamic regions (Andreasen, Rezai et al. 1992; Molina Rodriguez, Montz Andree et al. 1997; Sabri, Erkwoh et al. 1997).

With the enhanced resolution of MRI scanners, fMRI studies have afforded the field further opportunities to evaluate the functional correlates of negative symptoms. A recent and systematic review of the vast schizophrenia fMRI literature reported significant relationships between task-dependent activation of the ventrolateral prefrontal cortex and ventral striatum and negative symptom severity; that is, more severe negative symptoms were associated with reduced activation in both areas (Goghari, Sponheim et al. 2010). Interestingly, this review did not find support for the long-standing notion of DLPFC hypoactivity and its relationship with
negative symptoms (as demonstrated by the rCBF and cerebral metabolism studies discussed above). A subsequent study, however, found a significant relationship between diminished novelty-induced activation of the ventral striatum, premotor area, and DLPFC and higher negative symptom severity in individuals with schizophrenia (Wolf, Turetsky et al. 2008). Further, a study by Honey et al. (Honey, Pomarol-Clotet et al. 2005) demonstrated impaired functional connectivity between the anterior cingulate cortex and the supplementary motor area in individuals with schizophrenia with prominent negative symptoms.

In summary, numerous structural and functional imaging studies have been carried out in efforts to uncover the neurobiological substrates of the negative symptoms of schizophrenia. Although findings are not entirely consistent, these investigations collectively offer valuable insights into the potential neurobiological underpinnings of negative symptoms. The collective evidence suggests that negative symptoms are related to a hypoactive frontal lobe, and in particular to dysfunction within the OFC, ventrolateral prefrontal cortex, ventral striatum, DLPFC and some areas of the temporal lobe. The inconsistent findings across studies, however, likely reflect the heterogeneous nature of the illness, whereby some brain regions may be linked with negative symptoms in some patients but not in others.

1.8.2 Investigations of the deficit syndrome

Neurobiological investigations of the deficit syndrome have also been undertaken, with research into both the structural and functional correlates of this subgroup of patients with schizophrenia. The few structural imaging studies that have been conducted have found contradictory results: one study comparing deficit and non-deficit schizophrenia demonstrated significant reductions in prefrontal white matter volumes in the non-deficit group, while the deficit group was similar to
healthy controls; a second study found that patients with deficit schizophrenia had smaller total prefrontal lobe volumes, although they considered both gray and white matter volumes together and did not use the SDS for diagnostic categorization of the deficit group (reviewed in (Kirkpatrick, Buchanan et al. 2001)). A more recent study comparing deficit and non-deficit schizophrenia (as diagnosed by the SDS), and healthy controls did not demonstrate a significant difference in DLPFC volumes between deficit and non-deficit groups, although both groups had significantly smaller DLPFC volumes compared to healthy controls (Galderisi, Quarantelli et al. 2008). A DTI study investigating the integrity of the white matter tract connecting the frontal and parietal lobes in deficit and non-deficit syndrome, compared to healthy controls, found a significant reduction in white matter tract integrity in the deficit group compared to healthy controls, and a trend towards a reduction in tract integrity in the deficit compared to the non-deficit group (Rowland, Spieker et al. 2009). More recently, another DTI study comparing deficit syndrome, non-deficit syndrome, and matched healthy control participants revealed a specific white matter tract disruption, particularly in the right inferior longitudinal fasciculus, right arcuate fasciculus, and left uncinate fasciculus, in the deficit syndrome group, with non-deficit syndrome and healthy controls exhibiting equivalently intact white matter integrity (Voineskos, Foussias et al. 2013). Importantly, deficit and non-deficit groups did not differ in terms of cortical thickness, although both were significantly reduced compared to healthy controls, suggesting that the deficit syndrome may be uniquely characterized by white matter impairments. In addition, functional imaging studies using PET have also demonstrated that individuals with the deficit syndrome have reduced blood flow and glucose metabolism in the DLPFC compared to those with non-deficit schizophrenia and healthy controls (reviewed in (Kirkpatrick, Buchanan et al. 2001)).
1.8.3 Neurobiological correlates of specific negative symptoms in schizophrenia

With the accumulating evidence of associations between structural and functional brain abnormalities and the negative symptoms in schizophrenia, investigations have also been undertaken in efforts to delineate the neurobiology of specific negative symptoms. While there have not been any studies examining the diminished expression subdomain of negative symptoms, there has been limited exploration of the structural brain correlates of its component symptoms. Recent work has revealed associations between severity of alogia and reductions in cingulate cortex volumes (Makris, Seidman et al. 2010), as well as abnormalities in the bilateral uncinate fasciculi as determined by DTI (Szeszko, Robinson et al. 2008). Further, severity of affective flattening in individuals with schizophrenia has been associated with morphological abnormalities of the right anterior putamen surface (Ballmaier, Schlagenhauf et al. 2008), and with increased right hippocampal volume (Szendi, Kiss et al. 2006).

From a phenomenological perspective, the hedonic experience of individuals with schizophrenia has been demonstrated to be intact (as reviewed above). Functional neuroimaging, however, has presented a somewhat more complicated picture. Several groups have shown that individuals with schizophrenia, despite reporting equivalent hedonic experiences in laboratory settings to pleasant and unpleasant stimuli, exhibit mixed abnormalities in neural responses to these stimuli compared to healthy controls. These abnormalities have included: reduced activation of limbic and paralimbic regions (including the insula and nucleus accumbens), though with increased activation of extensive frontal cortical areas (Crespo-Facorro, Paradiso et al. 2001); reduced activation of orbitofrontal, medial, and dorsolateral prefrontal cortices, and amygdala (Paradiso, Andreasen et al. 2003); reduced activation in OFC and insula (Plailly, d'Amato et al. 2006); and, reduced ventral striatum and putamen activation although with no difference in other brain
regions (Dowd and Barch 2010). Further, a study investigating the neural responses to receipt of a reward did not show any differences between individuals with schizophrenia and healthy controls, including similar ventral striatal and OFC activation (Simon, Biller et al. 2010). A recent study also examined the functional neural correlates of self-reported physical anhedonia in individuals with schizophrenia, and found physical anhedonia severity to be related to reduced activation in medial prefrontal and orbitofrontal cortices, ventral striatum, and putamen activation (Harvey, Armony et al. 2010). Concerns about the validity of the PAS highlighted earlier, however, suggest cautious interpretation of these correlations.

Investigations into the neurobiological underpinnings of motivational deficits in schizophrenia have also provided valuable insights. From a structural neuroimaging perspective only one study has been carried out, which demonstrated that individuals with higher amotivation (i.e., a high apathy group as evaluated by the AES) exhibit significant reduction of bilateral frontal lobe volumes compared to a low amotivation group (Roth, Flashman et al. 2004). With regard to functional neural correlates of motivational deficits, several investigations have evaluated activation of the reward system, reward prediction, and the concept of “wanting” in individuals with schizophrenia. These studies have pointed towards the ventral striatum as playing a central role in reward prediction and reward anticipation; for example, individuals with schizophrenia exhibit blunted activation of the ventral striatum in response to reward-indicating cues, both when unmedicated and when treated with typical, but not atypical, antipsychotics (Juckel, Schlagenhauf et al. 2006; Juckel, Schlagenhauf et al. 2006; Schlagenhauf, Juckel et al. 2008), as well as abnormal striatal responses to reward-prediction errors (i.e., situations in which the reward obtained differs from that which was expected) (Waltz, Schweitzer et al. 2009). Further, both of these abnormalities in striatal response were correlated with negative symptom severity, and in the later case with amotivation severity specifically. In addition, the recent study by
Simon et al. (Simon, Biller et al. 2010) found that the degree of ventral striatal activation in subjects with schizophrenia during reward anticipation was inversely correlated with the severity of amotivation (as measured by the AES), although they did not corroborate others’ findings of differential striatal responses in schizophrenia and healthy control subjects.

Insights into the neurobiology of other domains deemed important for motivation and goal-directed behavior, including value and effort computations (i.e., cost-benefit analysis), and the process of generating and executing an action plan to pursue and achieve goals, have drawn upon examining these processes in normal controls. For example, investigations in the area of cognitive neuroscience have implicated a role for the OFC in the computation and representation of the value of particular goals, and the anterior cingulate along with its connections to the nucleus accumbens and forebrain in the determination of the effort or cost of pursuing a particular goal. Further, the generation and execution of action plans in pursuit of goals has been suggested to be carried out by the DLPFC (reviewed in (Barch and Dowd 2010)). Findings of structural and functional abnormalities in these same brain regions in schizophrenia, as well as associations between some of these areas with negative symptoms, have fueled speculation that these areas are critically related to the severity of motivational deficits in schizophrenia. The lack of studies following this line of investigation though, makes specific conclusions in this area quite tentative.

Overall, there has been a growing interest in the exploration of the neurobiological correlates of specific negative symptoms. Limited work into the etiology of diminished expression has suggested a role for the anterior cingulate in poverty of speech, as well as putamen and hippocampal involvement in affective flattening. A larger body of literature has examined the neurobiology of anhedonia, with paradoxical findings. Despite having intact subjective hedonic
experiences, individuals with schizophrenia appear to exhibit reductions in the activation of several prefrontal cortical regions and the ventral striatum in the context of receiving a reward. Similar examinations into the motivational deficits characteristic of schizophrenia have revealed relationships with reduced frontal lobe volumes, as well as with deficient activation of the ventral striatum in the context of amotivation and during reward prediction. Other important facets of motivational processes, including neurobiological correlates of cost-benefit computations and generation and execution of a goal-directed action plan, have yet to be investigated in schizophrenia.

1.8.4 The role of dopamine dysregulation in the negative symptoms of schizophrenia

Dopamine has figured prominently in conceptualizations of the neurochemical dysfunction that underlies the symptoms of schizophrenia. This was driven initially by the recognition of dopamine’s role in the development of psychotic symptoms, and the integral role of dopamine antagonism, specifically dopamine D₂ receptors (localized primarily in subcortical brain structures), that characterizes all known antipsychotic medications (reviewed in (Howes and Kapur 2009)). Recognition that D₂ antagonism offered little benefit in alleviating the cognitive and negative symptoms of schizophrenia, along with accumulating evidence of hypofrontality and its relationship with cognitive/negative symptoms, and the postulated role of dopamine D₁ receptors in PFC functioning contributed to a reconceptualization of dopamine’s role in schizophrenia. The revised model suggests that symptoms of schizophrenia result from a cortical/subcortical dopaminergic imbalance, with positive symptoms arising as a consequence of a subcortical hyperdopaminergic state, while negative symptoms represent the phenotypic expression of an underlying hypodopaminergic state (Davis, Kahn et al. 1991).
Dopamine’s role in the pathophysiology of negative symptoms was historically driven by the structural and functional imaging findings of associations between negative symptoms and abnormal findings in brain regions richly innervated by dopaminergic projections from the ventral tegmental area (VTA), in particular the PFC which forms the terminus of the mesocortical dopamine pathway. Neurochemical studies of PFC function and D₁ receptor binding (prominent in this region), however, have faced technological challenges limiting work in this area. To date, results have been inconsistent in linking PFC D₁ activity and negative symptoms (reviewed in (Guillin, Abi-Dargham et al. 2007; Howes and Kapur 2009)). Other studies have identified associations between negative symptoms and subcortical dopamine function, with blockade or reductions in density of striatal D₂ receptors being correlated with severity of negative symptoms, particularly affective flattening and amotivation (Martinot, Paillere-Martinot et al. 1994; Heinz, Knable et al. 1998). Once again, though, results have been inconsistent (Kessler, Woodward et al. 2009).

It remains, however, that advances in our understanding of dopamine’s role in motivational processes have offered valuable insights into the neurochemical basis of motivational deficits in schizophrenia. A wealth of recent evidence has established that dopamine is integral in motivation and “wanting”, in contrast to previously held notions of dopamine as a signal for the experience of pleasure or “liking”, which has since been linked to activation of opioid and gamma amino butyric acid (GABA) systems (Berridge 2007). Further refinements in our understanding of motivation have revealed that dopamine plays a central role in reward prediction, mediated by dopaminergic projections from the VTA to ventral and dorsal striatal regions, that appears essential for learning and updating reward associations and the predictability of rewards (Schultz 2002). Further, striatal dopamine has been found to play a role in determining the effort required to achieve a goal or reward as part of a cost-benefit analysis.
process. Specifically, dopamine depletion in the nucleus accumbens results in animals choosing low effort/low reward over high effort/high reward options (reviewed in (Barch and Dowd 2010)). Extension of this work to schizophrenia has focused primarily on reward prediction through examination of neural responses to reward-predicting cues. In addition to reduced ventral striatal activation in response to reward cues (discussed above), there is evidence that D2 antagonism is directly related to this reduction in ventral striatal activation, with implications regarding the origins of both primary and secondary amotivation (Kirsch, Ronshausen et al. 2007; Schlagenhauf, Juckel et al. 2008). These conclusions arise from comparisons between patients treated with typical and atypical antipsychotics, with the assumption that D\textsubscript{2} receptor binding is higher with typical antipsychotics; however, no direct measurement of D\textsubscript{2} receptor occupancy was undertaken.

In short, investigations of the neurochemical basis of negative symptoms in schizophrenia have focused primarily on the role of dopamine, in large part due to the prominence of the dopamine hypothesis of schizophrenia, as well as evidence suggestive of a hypodopaminergic state in frontal cortical regions and its possible link with negative symptoms. Despite initial speculation, the role of the D\textsubscript{1} receptor in negative symptoms has produced inconsistent findings. Other studies, though, have endorsed a role for subcortical dopamine in negative symptoms, especially dopamine signaling in the striatum and its impact on reward prediction and deficits therein. Dopamine has also been implicated in other facets of motivation, although investigations in schizophrenia are lacking. There has also been emerging evidence for the role of other neurotransmitter systems, and in particular glutamate, in the pathophysiology of schizophrenia (Javitt 2007), although their specific role in the etiology of negative symptoms is yet to be determined.
1.8.5 Neurobiological correlates of negative symptoms in the schizophrenia spectrum

Substantially less research has been conducted examining the neurobiological correlates of negative symptoms across the schizophrenia spectrum. Structural imaging studies of individuals classified as being at ultra-high risk of conversion to psychosis have demonstrated an association between more severe negative symptoms in the prodrome and reduced insular cortex volume (Takahashi, Wood et al. 2009), as well as thinning of the anterior cingulate cortex in individuals that go on to develop psychosis (Fornito, Yung et al. 2008). Emerging multimodal imaging studies have demonstrated dopaminergic dysfunction in individuals at high risk of developing psychosis that may be linked to cognitive dysfunction observed in this population, although specific relationships with negative symptoms have not been reported to date (Fusar-Poli, Howes et al. 2009; Fusar-Poli, Howes et al. 2010).

In schizotypy, structural imaging studies have report reductions in frontal and temporal lobe volumes in SPD that are intermediate between those found in schizophrenia and healthy controls (Hazlett, Buchsbaum et al. 2008). Such reductions, although significantly associated with negative symptom severity in schizophrenia, are not associated with negative symptoms in schizotypy. In contrast, reduction in cingulate (Hazlett, Buchsbaum et al. 2008) and frontal lobe volume (Raine, Sheard et al. 1992; Siever and Davis 2004) have been correlated with negative symptoms in schizotypy. A further report noted a significant relationship between reduced caudate volume and severity of negative symptoms in female subjects with SPD (Koo, Levitt et al. 2006). Studies in SPD have also reported abnormal frontal lobe activation similar to schizophrenia although links with discrete negative symptoms have not been identified (reviewed in (Phillips and Seidman 2008)). There is emerging evidence of dopaminergic
dysfunction in SPD, with the suggestion that reduced dopaminergic activity may also be associated with negative symptoms in SPD (Siever and Davis 2004).

1.9 Outline of Experiments

Chapter 2 will provide a background and rationale for the four manuscripts included in this PhD thesis, along with their objectives and hypotheses. The first two studies (Chapters 3 and 4) have been published in a peer-reviewed journal – *Schizophrenia Research*. The remaining two studies (Chapters 5 and 6) will be submitted to peer-reviewed journals for publication. As the studies that comprise each of the chapters exist as stand-alone articles, material presented in each of these chapters may overlap with material in other chapters, as well as the Introduction and Discussion sections of this thesis.
Chapter 2

2 Overview of Experiments and Hypotheses

This thesis consists of three papers that advance our understanding of the cross-sectional and longitudinal determinants of community functioning in schizophrenia, with a particular focus on negative symptoms. In addition, a fourth paper offers insights into the relationships between motivational deficits, effort exerted during cognitive testing, and cognitive test performance in schizophrenia.

2.1 Study One: Motivational Deficits as the Central Link to Functioning in Schizophrenia: A Pilot Study

2.1.1 Background

Negative symptoms have consistently been found to contribute to functional impairment in schizophrenia, above and beyond the impact of cognitive deficits. However, studies have routinely evaluated negative symptoms as a whole, or alternatively, discrete aspects of negative symptoms in isolation. In light of this, the pilot study described here sought to further delineate the core negative symptoms that impact functional outcomes in schizophrenia through an examination of the concurrent contribution of motivational and pleasure deficits, along with diminished expression and cognitive deficits, to the prediction of cross-sectional functioning in schizophrenia. To our knowledge, this was the first study at the time to address this question in the literature.
2.1.2 Hypotheses

We hypothesized that motivational deficits would serve as the most important predictor of functioning in schizophrenia. However, given the findings for cognitive deficits and anticipatory pleasure, and their correlation with functioning, we hypothesized that these two symptoms would serve as additional predictors of cross-sectional functioning.

2.2 Study Two: Prediction of Longitudinal Functional Outcomes in Schizophrenia: The impact of baseline motivational deficits

2.2.1 Background

Emerging evidence has suggested that motivational deficits are a central component of negative symptoms in schizophrenia, and have been linked to the functional impairment characterizing this illness. Our previous pilot study revealed that motivational deficits served as the critical predictor of cross-sectional functioning in schizophrenia, with no significant contribution from other symptom domains. The aim of the present study was to extend our previous cross-sectional findings by examining the concurrent contribution of baseline motivational deficits, other negative symptoms, and other important symptom domains on functional outcomes in the same stable outpatients with schizophrenia from our original pilot study, assessed at 6-month follow-up.

2.2.2 Hypotheses

Based on our previous cross-sectional findings, we hypothesized that baseline motivational deficits would continue to serve as the most important predictor of functioning for stable
outpatients with schizophrenia 6-months later. We also hypothesized that, among all the other symptoms of schizophrenia, cognitive deficits would offer additional predictive value for longitudinal functioning.

2.3 Study Three: The Determinants of Community Functioning in Schizophrenia: A one-year longitudinal investigation of the role of negative symptoms and cognitive deficits

2.3.1 Background

Impairment in community functioning has long been recognized as a characteristic feature of schizophrenia, with recent work highlighting the important role for both negative symptoms and cognitive deficits in determining functional outcomes in schizophrenia. Moreover, within negative symptoms, motivational deficits have been found to be particularly important contributors to the impairment in community functioning seen in schizophrenia. Extending our previous findings, we sought to investigate the concurrent contribution of discrete negative symptoms, cognition, positive symptoms, and depression in the determination of longitudinal community functioning in schizophrenia over the course of one year. Specifically, we sought to examine the stability of our previous cross-sectional findings with regards to motivational deficits in a larger population of stable outpatients with schizophrenia, as well as to investigate the predictors of longitudinal community functioning, both for global functioning and within discrete domains of community functioning.
2.3.2 Hypotheses

We hypothesized that motivational deficits would show a stable contribution to the prediction of community functioning assessed cross-sectionally at three time points over the course of one year. Further, we hypothesized that motivational deficits would continue to serve as the most reliable predictor of longitudinal functioning in schizophrenia, with an important predictive role across discrete domains of community functioning. Finally, based on our previous findings, as well as emerging findings from the field, we hypothesized that cognitive deficits would show smaller, and inconsistent, predictive value for longitudinal community functioning in schizophrenia.

2.4 Study Four: Motivated to do well: Exploration of the relationships between motivation, effort, and cognitive test performance in schizophrenia

2.4.1 Background

The relationship between negative symptoms and cognitive deficits in schizophrenia has frequently raised questions around the nature of their relationship. This has been particularly true for motivational deficits, with the possibility that cognitive impairments seen in schizophrenia are driven by a lack of motivation to do well on cognitive testing. Some findings have suggested that motivation may impact cognitive test performance, related specifically to low effort being exerted during cognitive testing. In this study, we sought to further our understanding of the relationship between motivation and cognition in schizophrenia, both for global cognitive performance and across specific cognitive subdomains. Further, we sought to clarify the relationship of effort during cognitive testing with motivation and cognition. Finally,
we sought to investigate whether poor performance on effort testing was driven by a lack of motivation or cognitive dysfunction in schizophrenia.

2.4.2 Hypotheses

We hypothesized that motivation would be significantly correlated with cognitive performance in schizophrenia, although based on previous findings, that there would be a differential relationship across subdomains of cognition. We also hypothesized that effort during cognitive testing would be significantly related to clinical measures of motivation, and that those individuals exhibiting low effort would be characterized by more severe motivational deficits. Finally, we hypothesized that motivational deficits would be the most significant predictor of effort test performance.
3 Motivational Deficits as the Central Link to Functioning in Schizophrenia: A Pilot Study

Abstract

Negative symptoms have consistently been found to contribute to functional impairment in schizophrenia. In this pilot study, we sought to delineate the core negative symptoms that contribute to this functional impairment. Adult outpatients with schizophrenia were evaluated for the severity of positive, negative, cognitive, and depressive symptoms. The Quality of Life Scale was used to assess current functioning. Results from 21 participants revealed that amotivation was the sole predictor of functioning, accounting for 74% of the variance in current functioning. This suggests that motivational deficits are the central link between negative symptoms and functional impairment in schizophrenia.
3.2 Introduction

The recognition and later characterization of negative symptoms as a core component of schizophrenia dates back to the earliest descriptions of Kraepelin and Bleuler, who each highlighted the central role of avolition (i.e., amotivation) in the phenomenology and course of this illness (Kraepelin 1919; Bleuler 1950). More recently, the NIMH consensus statement on negative symptoms states that negative symptoms consist of blunted affect, poverty of speech, asociality and anhedonia, and avolition and apathy (Kirkpatrick, Fenton et al. 2006).

Closer examination of the negative symptom construct has revealed the existence of two key subdomains: 1) Diminished expression, including blunted affect and poverty of speech; and 2) Amotivation, including avolition/apathy and anhedonia/asociality (Mueser, Sayers et al. 1994; Sayers, Curran et al. 1996; Kelley, van Kammen et al. 1999; Peralta and Cuesta 1999; Kimhy, Yale et al. 2006). Of note, discrepant findings have called into question the presence of anhedonia in schizophrenia; for example, neuroimaging studies have revealed abnormal neural responses to pleasant stimuli in schizophrenia (Crespo-Facorro, Paradiso et al. 2001; Paradiso, Andreasen et al. 2003; Plailly, d'Amato et al. 2006). In contrast, other studies have found that individuals with this illness report intact consummatory pleasure (i.e., pleasure derived from engaging in pleasurable activities), yet exhibit deficits in anticipatory pleasure (i.e., pleasure derived from anticipating that an activity will be enjoyable) (Berenbaum and Oltmanns 1992; Kring, Kerr et al. 1993; Kring and Neale 1996; Burbridge and Barch 2007; Gard, Kring et al. 2007; Heerey, Robinson et al. 2007).

Investigations of the correlates of functional outcomes in schizophrenia have consistently revealed significant cross-sectional relationships with negative symptoms, above and beyond the contribution of cognitive dysfunction, and in particular suggest a role for amotivation and
anticipatory pleasure (Sayers, Curran et al. 1996; Ho, Nopoulos et al. 1998; Blanchard, Horan et al. 2005; Milev, Ho et al. 2005; Rosenheck, Leslie et al. 2006; Gard, Kring et al. 2007) reviewed in (Foussias and Remington 2008). However, these studies have examined negative symptoms as a whole, or alternatively, discrete aspects of the negative symptom construct in isolation. In light of this, we sought to further delineate the core negative symptoms that impact functional outcomes in schizophrenia through an examination of the concurrent contributions of motivational and pleasure deficits, diminished emotional expression, and cognitive deficits to functioning in this population. To our knowledge, this has yet to be addressed in the research literature.

3.3 Methods

3.3.1 Participants

Individuals between the ages of 18 and 55 with a DSM-IV diagnosis of Schizophrenia, determined by the Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies (MINI) (Sheehan, Lecrubier et al. 1998), were recruited at the Centre for Addiction and Mental Health, Toronto, Canada. All participants were outpatients on stable doses of antipsychotic medications for at least 4 weeks. Participants were excluded from the study if they: met criteria for substance abuse or dependence within the past 3 months, or other DSM-IV Axis I disorders apart from Schizophrenia; had a history of neurological disease; were experiencing significant akathisia (a rating of > 2 on the Barnes Akathisia Rating Scale Global item (Barnes 1989)), or significant extrapyramidal symptoms (a rating of > 2 on more than 2 items of the Simpson Angus Rating Scale (Simpson and Angus 1970)).
3.3.2 Instruments and Procedures

Positive and negative symptom severity was evaluated with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982), respectively. Motivational deficit was assessed with the Apathy Evaluation Scale – Clinician version (AES) (Marin, Biedrzycki et al. 1991), while anticipatory and consummatory pleasure was assessed with the self-report Temporal Experience of Pleasure Scale (TEPS) (Gard, Gard et al. 2006). Depressive symptoms were evaluated with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington et al. 1990). Cognitive functioning was measured with the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe, Goldberg et al. 2004). Functional status, the primary outcome of interest, was assessed with the Quality of Life Scale (QLS) (Heinrichs, Hanlon et al. 1984). Following diagnostic assessment participants were evaluated in a single study visit by one of two trained raters (S.M. or G.F.), whose interrater agreement (i.e., scores within 1 point between raters) was over 80%. This study was approved by the local research ethics board, and all participants provided informed consent.

3.3.3 Analysis

Statistical analysis was performed using SPSS v.16 for Mac (SPSS Inc.). Examination of the relationships between symptoms and functional status in participants with schizophrenia was conducted through stepwise multiple regression. Negative symptoms were separated into their 2 core subdomains: Diminished Expression and Amotivation (reviewed in (Foussias and Remington 2008). The SANS Diminished Expression subdomain was comprised of the SANS Affective Flattening subscale and the Poverty of Speech item (excluding inappropriate affect,
poverty of content of speech, blocking, response latency, and global items). The SANS Amotivation subdomain was comprised of the SANS Avolition-Apathy and Anhedonia-Asociality subscales (excluding global items). The BACS composite score, transformed into a standardized $Z$ score based on age and sex normative data, was used as a measure of global cognitive function. Functional status was the mean score of all QLS items. Evaluation of assumptions of multiple regression modeling was performed and did not reveal any violations.

Given the concerns with the use of stepwise regression (Tabachnick and Fidell 1996), we also conducted hierarchical regression of predictors based on theoretical models of determinants of functional outcome in schizophrenia (Table 3-1). Models were compared using the Akaike Information Criterion (AIC; (Akaike 1974)). Finally, due to overlap in item content between the Intrapsychic Foundations subscale of the QLS and negative symptom measures, mean QLS scores were recalculated after exclusion of this subscale, and stepwise regression analysis was repeated.

### 3.4 Results

Twenty-one participants with a mean age of 39.5 years and a mean duration of illness of 13.7 years were included in this pilot study. Means and standard deviations of symptom and function measures are shown in Table 3-2.

Stepwise regression revealed that amotivation, measured by the AES and the SANS Amotivation subdomain, was a highly significant predictor of functional status ($R^2 = 0.74$, adjusted $R^2 = 0.71$, $p = 0.011$), and accounted for 74% of the variance in QLS scores. Amotivation measured by the AES accounted for 62% of the variance ($R^2$ change = 0.62), and was the most influential
predictor of functional status (beta = -0.52, p = 0.003), followed by SANS Amotivation which accounted for an additional 12% of the variance ($R^2$ change = 0.12, beta = -0.44, p = 0.011). Bivariate correlations for AES and SANS Amotivation with functional status are shown in *Figure 3-1*, while bivariate correlations for all measures in this study are shown in *Table 3-3*. Other symptom measures did not significantly contribute to the prediction of functional status above and beyond motivational deficits.

Subsequent hierarchical regression for each theoretical model (*Table 3-1*) revealed that Model 1 was the most parsimonious (i.e., lowest AIC), and reinforced the initial stepwise regression result that amotivation was the best predictor of functional status in this population. Model 2 provided equivalent overall prediction, and with an equivalent AIC, though entry of SANS Amotivation first resulted in lower initial explanation of variance in QLS score.

Finally, stepwise regression after exclusion of the Intrapsychic Foundations subscale of the QLS revealed similar findings to the initial analysis. Amotivation continued to be a highly significant predictor of functional status ($R^2 = 0.65$, adjusted $R^2 = 0.61$, p = 0.023). Other symptom measures did not offer any additional explanation of variance in functional status.

### 3.5 Conclusions

Negative symptoms have been implicated in the poor functional outcomes of individuals with schizophrenia. The results of this pilot investigation take this issue a step further, examining different aspects of the negative symptom domain. To this end, we found that motivational deficits were strongly predictive of current functioning, accounting for 74% of the variance in functioning in individuals with schizophrenia. The expressive component of negative symptoms,
however, did not offer any additional contribution above that provided by motivational deficits. Similarly, measures of anticipatory and consummatory pleasure, positive symptoms, depression, and global cognitive functioning did not contribute to the prediction of functioning.

One limitation of this pilot study is its small sample size, which may have hindered its ability to detect significant influences from other important symptom domains. That being said, it was sufficient to reveal a substantive effect between motivational deficits and functioning in schizophrenia. Further, raters were not blinded, as independent and dependent variables were evaluated simultaneously. Finally, the subjective nature of clinical assessment and self-report serves as a limitation not only within this study, but for schizophrenia research more broadly concerned.

The relationship between motivational deficits and functioning in schizophrenia demonstrated here is consistent with previous reports that have highlighted the importance of motivational deficits in this illness (Heerey and Gold 2007; Waltz, Frank et al. 2007) and their role in functioning (Sayers, Curran et al. 1996; Kiang, Christensen et al. 2003). Interestingly, this relationship between amotivation and poor functioning is also consistent with findings in other populations (reviewed in (van Reekum, Stuss et al. 2005)). The results of this pilot study, however, did not support a role for anticipatory pleasure (Gard, Kring et al. 2007), expressive deficits (Gur, Kohler et al. 2006), or cognition (Green, Kern et al. 2000) in determining functioning in schizophrenia. In keeping with historical conceptualizations of this illness, these findings collectively offer preliminary support for the centrality of amotivation (i.e., avolition) as the essence of schizophrenia, particularly as it relates to functional outcomes (Foussias and Remington 2008). Other symptoms including expressive and pleasure deficits, and at times
cognitive dysfunction (Gorissen, Sanz et al. 2005), may represent phenotypic expressions of this core avolition.

The emergence of an NIMH initiative focusing on evaluation and treatment of negative symptoms highlights the longstanding recognition of the importance of these symptoms in determining the course and functional outcome of schizophrenia (Kirkpatrick, Fenton et al. 2006). The results of the present study suggest that motivational deficits serve as the central link between negative symptoms and poor functioning in schizophrenia. In the ongoing search for strategies to alter the longitudinal course and functional outcome of schizophrenia, the present findings suggest that increased focus on motivational deficits is necessary to effect these changes.
Table 3-1. Hierarchical Regression Models

<table>
<thead>
<tr>
<th>Step</th>
<th>Model</th>
<th>Beta</th>
<th>R² Change</th>
<th>p</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>AES</td>
<td>-52.62</td>
<td>.003</td>
<td>-12.97</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>SANS</td>
<td>-52.44</td>
<td>.011</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>SANS</td>
<td>-52.17</td>
<td>.008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>SANS</td>
<td>-52.03</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>SANS</td>
<td>-52.00</td>
<td>.003</td>
<td></td>
</tr>
</tbody>
</table>

(Abbreviations: AES – Apathy Evaluation Scale; SANS – Scale for the Assessment of Negative Symptoms; SANS-A – SANS Amotivation Subdomain; SANS-DE – SANS Diminished Expression Subdomain; TEPS-Ant – Temporal Experience of Pleasure Scale – Anticipatory Pleasure subscale; BACS – Brief Assessment of Cognition in Schizophrenia; ns – non-significant; AIC – Akaike Information Criterion)
Table 3-2. Subject Demographics

<table>
<thead>
<tr>
<th></th>
<th>Mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>39.5 (9.2)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>17 : 4</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>13.7 (10.5)</td>
</tr>
<tr>
<td>SAPS Total score</td>
<td>16.4 (13.9)</td>
</tr>
<tr>
<td>SANS Total score</td>
<td>17.4 (12.5)</td>
</tr>
<tr>
<td>AES Total score</td>
<td>35.9 (9.5)</td>
</tr>
<tr>
<td>TEPS Anticipatory Pleasure Score</td>
<td>42.4 (7.5)</td>
</tr>
<tr>
<td>TEPS Consummatory Pleasure Score</td>
<td>33.6 (6.9)</td>
</tr>
<tr>
<td>CDSS Total Score</td>
<td>1.9 (2.3)</td>
</tr>
<tr>
<td>BACS Composite Z-score</td>
<td>-1.4 (1.1)</td>
</tr>
<tr>
<td>QLS Total score</td>
<td>3.1 (1.3)</td>
</tr>
</tbody>
</table>

(Abbreviations: SAPS – Scale for the Assessment of Positive Symptoms; SANS - Scale for the Assessment of Negative Symptoms; AES - Apathy Evaluation Scale; TEPS - Temporal Experience of Pleasure Scale; CDSS - Calgary Depression Scale for Schizophrenia; BACS - Brief Assessment of Cognition in Schizophrenia; QLS – Quality of Life Scale)
### Table 3-3. Bivariate Correlations

<table>
<thead>
<tr>
<th>Measure</th>
<th>QLS Total Score (r)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SANS Amotivation</td>
<td>-0.75</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>SANS Diminished Expression</td>
<td>-0.50</td>
<td>.020</td>
</tr>
<tr>
<td>AES Total</td>
<td>-0.79</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>TEPS Anticipatory Pleasure</td>
<td>0.25</td>
<td>ns</td>
</tr>
<tr>
<td>TEPS Consummatory Pleasure</td>
<td>0.21</td>
<td>ns</td>
</tr>
<tr>
<td>BACS Composite score</td>
<td>0.21</td>
<td>ns</td>
</tr>
<tr>
<td>SAPS Total</td>
<td>-0.28</td>
<td>ns</td>
</tr>
<tr>
<td>CDSS</td>
<td>-0.26</td>
<td>ns</td>
</tr>
</tbody>
</table>

(Abbreviations: See Table 2. ns – non-significant)
Figure 3-1. Bivariate correlations between amotivation and current functioning.

A

\[ r = -0.79 \]
\[ p < 0.001 \]
Amotivation measured by (A) the AES; and (B) the SANS Amotivation subdomain. (AES: Apathy Evaluation Scale; SANS: Scale for the Assessment of Negative Symptoms; QLS: Quality of Life Scale.)
Chapter 4

4 Prediction of Longitudinal Functional Outcomes in Schizophrenia: The impact of baseline motivational deficits

Contents of this chapter have been published as:


Prediction of longitudinal functional outcomes in schizophrenia:

The impact of baseline motivational deficits.


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4.1 Abstract

Emerging evidence suggests that motivational deficits are a central component of negative symptoms in schizophrenia, and linked to functional impairment characterizing this illness. This study extends previous cross-sectional findings by examining the concurrent contributions of baseline motivational deficits, other negative symptoms, and other symptom domains on longitudinal functional outcomes in schizophrenia. Results of this longitudinal examination of 18 patients from our previous pilot study reveal that amotivation accounts for 74% and 72% of the variance in functional outcomes at baseline and 6-month follow-up, respectively. These findings further suggest a fundamental role for motivational deficits in predicting functional outcomes in schizophrenia.
4.2 Introduction

Advances in our understanding of the phenomenology of negative symptoms in schizophrenia have offered valuable insights into the underlying structure of these symptoms and their functional consequences. The recent NIMH consensus definition of negative symptoms highlights several symptoms including blunted affect, poverty of speech, asociality and anhedonia, and avolition and apathy (Kirkpatrick, Fenton et al. 2006). Additional work has shown the existence of two key negative symptom subdomains: 1) Diminished expression (blunted affect and poverty of speech); and 2) Amotivation, (avolition/apathy and anhedonia/asociality) (Mueser, Sayers et al. 1994; Sayers, Curran et al. 1996; Kelley, van Kammen et al. 1999; Peralta and Cuesta 1999; Kimhy, Yale et al. 2006).

Cross-sectional studies have consistently demonstrated relationships between negative symptoms and functional impairments in schizophrenia, above and beyond the role of cognitive deficits (Ho, Nopoulos et al. 1998; Blanchard, Horan et al. 2005; Milev, Ho et al. 2005; Rosenheck, Leslie et al. 2006). Discrete negative symptom subdomains have also been investigated, with findings to date suggesting a central role of motivational deficits and anticipatory pleasure (Foussias and Remington 2010). Moreover, recent cross-sectional and longitudinal studies in first-episode and chronic schizophrenia have shown that motivational deficits are significantly related to functional outcomes in these populations (Kiang, Christensen et al. 2003; Nakagami, Xie et al. 2008; Faerden, Friis et al. 2009; Faerden, Finset et al. 2010). A recent pilot study from our group suggested that in the context of the myriad of symptoms that individuals with schizophrenia experience, motivational deficits are the most important predictor of current functional status, accounting for 74% of the variance (Foussias, Mann et al. 2009). In an effort
to further our understanding of the predictors of functional outcomes in schizophrenia, we sought to evaluate the role of baseline symptoms in predicting longitudinal functioning. Specifically, we sought to examine the concurrent contribution of discrete negative symptom subdomains, along with other important symptom domains, on longitudinal functioning in schizophrenia.

4.3 Methods

4.3.1 Participants

21 individuals between the ages of 18 and 55 with a DSM-IV diagnosis of Schizophrenia, determined by the Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies (MINI) (Sheehan, Lecrubier et al. 1998), were recruited at the Centre for Addiction and Mental Health, Toronto, Canada, between May and November 2008. Inclusion in this study also required that participants were outpatients on stable antipsychotic medication doses for at least 4 weeks. Participants were excluded if they: met criteria for substance abuse or dependence within the past 3 months, or other DSM-IV Axis I disorders apart from Schizophrenia; had a history of neurological disease; had significant akathisia (a rating of > 2 on the Barnes Akathisia Rating Scale Global item (Barnes 1989)), or significant extrapyramidal symptoms (a rating of > 2 on more than 2 items of the Simpson Angus Rating Scale (Simpson and Angus 1970)). In total, 31 potential participants were approached, with 9 individuals not meeting study criteria, and 1 declining to participate during initial screening.
4.3.2 Instruments and Procedures

Positive and negative symptom severity was evaluated with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982), respectively. Motivational deficit was assessed with the Apathy Evaluation Scale – Clinician version (AES) (Marin, Biedrzycki et al. 1991), an instrument that has been used previously in first-episode and chronic schizophrenia populations for this purpose (Kiang, Christensen et al. 2003; Foussias, Mann et al. 2009; Faerden, Finset et al. 2010). Anticipatory and consummatory pleasure were assessed with the self-report Temporal Experience of Pleasure Scale (TEPS) (Gard, Gard et al. 2006). Depressive symptoms were evaluated with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington et al. 1990), and cognitive functioning with the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe, Goldberg et al. 2004). Functional status was assessed with the Quality of Life Scale (QLS) (Heinrichs, Hanlon et al. 1984), chosen because of its widespread use as a functional outcome measure in schizophrenia trials, including the two large antipsychotic effectiveness trials, thus allowing for a meaningful and recognizable metric of functioning in this population (Lieberman, Stroup et al. 2005; Jones, Barnes et al. 2006). Following diagnostic assessment participants were evaluated for symptom severity and functional status at baseline and at 6-month follow-up. Baseline assessments were done by one of two trained raters (S.M. or G.F.), while at 6-months, participants were evaluated for symptoms severity and functional status by two independent raters blind to baseline status. Inter-rater agreement (i.e., scores within 1 point between raters) was over 80%. This study was approved by the local research ethics board, and all participants provided informed consent.
4.3.3 Analysis

Statistical analysis was performed using SPSS v.16 (SPSS Inc.). Examination of the relationships between baseline symptoms and functional status at baseline and 6-month follow-up was conducted through stepwise multiple regression, with functional status as the dependent variable, and symptom domains as the independent variables. Bivariate correlational analyses were conducted to evaluate the relationship between symptom domains of interest and functional outcomes at both baseline and 6-month follow-up. The SANS Diminished Expression subdomain was comprised of the SANS Affective Flattening subscale and the Poverty of Speech item (excluding inappropriate affect, poverty of content of speech, blocking, response latency, and global items). The BACS composite Z score, based on age and sex normative data, was the measure of global cognitive function. Functional status was the mean score of all QLS items. In addition, due to overlap in item content between the Intrapsychic Foundations subscale of the QLS and negative symptom measures, mean QLS scores were recalculated after exclusion of this subscale, and stepwise regression analysis repeated. Evaluation of the data for normality, linearity, and homoscedasticity did not reveal any violations of the assumptions of multiple regression modeling. Further, examinations for multicollinearity through the Conditioning Index, Variance Proportions, and Variance Inflation Factor, did not reveal any evidence of multicollinearity.

4.4 Results

Eighteen of the 21 participants recruited and described in our original pilot study were available for evaluation at 6-month follow-up. These participants had a mean age of 41 years and mean duration of illness of 14 years. Summary demographic and clinical variables are shown in Table
Bivariate correlations for all measures with functional status scores at both time points are shown in Table 4-2.

The results of stepwise regression (Table 4-3) revealed that amotivation, measured by the AES, was the most influential predictor of functional status both at baseline ($R^2 = 0.743$, adjusted $R^2 = 0.727$, beta = -0.740, $p < 0.001$) and at 6-month follow-up ($R^2 = 0.721$, adjusted $R^2 = 0.703$, beta = -0.888, $p < 0.001$), accounting for 74% and 72% of the variance in QLS scores at baseline and follow-up, respectively. Further, at baseline SAPS total score contributed an additional 8% of explained variance in functional status. At 6-month follow-up, aside from amotivation, only CDSS score explained significant (9%) additional variance in functional status. Secondary analysis after exclusion of the Intrapsychic Foundations subscale of the QLS revealed similar findings (Table 4-4). Amotivation continued to be the most influential predictor of functional status at both baseline and 6-month follow-up, with much smaller contributions to explained variance in functional status by positive and depressive symptoms.

4.5 Conclusions

We sought to evaluate the concurrent contribution of baseline symptoms in predicting longitudinal functioning in schizophrenia. Our results reveal a consistent relationship between negative symptoms and poor functional outcomes in schizophrenia, with motivational deficits emerging as the most influential predictor of functioning cross-sectionally and at 6 months. These findings are in line with other reports demonstrating that motivational deficits are significantly related to functional outcomes in schizophrenia (Kiang, Christensen et al. 2003; Nakagami, Xie et al. 2008; Faerden, Friis et al. 2009; Faerden, Finset et al. 2010). Importantly, these studies used different measures of functional status, including the Global Assessment of
Functioning – functioning score, the Independent Living Skills Survey, and the Role Functioning Scale. Other symptom domains including positive and depressive symptoms appear to make some small contribution, though not reliably. Interestingly, other components of negative symptoms (i.e., diminished expression and the experience of pleasure) do not offer any additional predictive value above and beyond amotivation, in contrast to previous reports (Gur, Kohler et al. 2006; Gard, Kring et al. 2007). Further, cognitive deficits did not appear to make a significant contribution to the prediction of functional status in schizophrenia, a finding which is in keeping with some (Milev, Ho et al. 2005; Rosenheck, Leslie et al. 2006), but not other investigations (Green, Kern et al. 2004), and may reflect the heterogeneity of cognitive impairment inherent to the illness (Heinrichs and Zakzanis 1998).

Limitations of this preliminary longitudinal study include its small sample size, which may have limited our ability to detect the contributory role of other symptom domains, although it was sufficient to reveal a consistent and large effect for motivational deficits. Further, baseline assessments of independent and dependent variables were conducted by a single rater. Follow-up assessments, however, were carried out by independent raters blind to baseline status. In addition, regression analyses can establish associations between factors, but cannot determine the direction of causation. Further, while there are concerns around the overlap between measures of motivation and functioning as measured by the QLS, the AES also evaluates cognitive and emotional facets of motivated behavior, rather than solely relying on behavioral proxies for these internal experiences, suggesting that it measures a distinct construct from functioning as measured by the QLS, particularly after exclusion of the intrapsychic foundations subscale. The absence of multicollinearity reinforces this position. Finally, the subjective nature of clinical assessments serves as a limitation for both this study and the field of schizophrenia research in general.
Historical notions of schizophrenia’s psychopathology, dating back to the earliest descriptions by Kraepelin and Bleuler, held that amotivation (i.e., avolition) was central to its phenomenology and course (Kraepelin 1919; Bleuler 1950). Our present findings offer additional support for the figural role of amotivation among the negative symptoms, particularly in predicting the characteristic functional impairment seen in schizophrenia. In the ongoing search for strategies to alter the longitudinal course and functional outcomes for those with schizophrenia, the present findings suggest that greater understanding of motivational deficits, their neurobiological underpinnings, and interventions geared towards improving motivated behavior, are necessary components to effect these changes.
Table 4-1. Subject Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.4 (8.5)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>14 : 4</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>14.1 (10.8)</td>
</tr>
<tr>
<td>Atypical : Typical Antipsychotic Medication</td>
<td>15 : 3</td>
</tr>
<tr>
<td>CPZ Equivalents (mg)(^1)</td>
<td>451 (205)</td>
</tr>
<tr>
<td>SAPS Total score</td>
<td>15.7 (14.4)</td>
</tr>
<tr>
<td>SANS Total score</td>
<td>18.8 (12.8)</td>
</tr>
<tr>
<td>AES Total score</td>
<td>36.0 (10.3)</td>
</tr>
<tr>
<td>TEPS Anticipatory Pleasure Score</td>
<td>42.3 (7.9)</td>
</tr>
<tr>
<td>TEPS Consummatory Pleasure Score</td>
<td>33.2 (7.3)</td>
</tr>
<tr>
<td>CDSS Total Score</td>
<td>1.9 (2.4)</td>
</tr>
<tr>
<td>BACS Composite Z-score</td>
<td>-1.29 (1.1)</td>
</tr>
<tr>
<td>QLS Total score @ baseline</td>
<td>3.0 (1.2)</td>
</tr>
<tr>
<td>QLS Total score @ 6-months</td>
<td>2.8 (1.4)</td>
</tr>
</tbody>
</table>

(Abbreviations: CPZ – Chlorpromazine; SAPS – Scale for the Assessment of Positive Symptoms; SANS - Scale for the Assessment of Negative Symptoms; AES - Apathy Evaluation Scale; TEPS - Temporal Experience of Pleasure Scale; CDSS - Calgary Depression Scale for Schizophrenia; BACS - Brief Assessment of Cognition in Schizophrenia; QLS – Quality of Life Scale. \(^1\)CPZ equivalents were determined based on (Kane, Aguglia et al. 1998; Andreasen, Pressler et al. 2010).)
**Table 4-2. Bivariate Correlations**

<table>
<thead>
<tr>
<th></th>
<th>QLS Total Score @ baseline (r)</th>
<th>QLS Total Score @ 6 months (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES Total score</td>
<td>-0.86**</td>
<td>-0.85**</td>
</tr>
<tr>
<td>SANS Diminished Expression</td>
<td>-0.46</td>
<td>-0.55*</td>
</tr>
<tr>
<td>BACS Composite score</td>
<td>0.24</td>
<td>0.16</td>
</tr>
<tr>
<td>TEPS Anticipatory Pleasure</td>
<td>0.28</td>
<td>0.30</td>
</tr>
<tr>
<td>TEPS Consummatory Pleasure</td>
<td>0.19</td>
<td>0.28</td>
</tr>
<tr>
<td>SAPS Total score</td>
<td>-0.47*</td>
<td>-0.41</td>
</tr>
<tr>
<td>CDSS Total score</td>
<td>-0.24</td>
<td>-0.34</td>
</tr>
<tr>
<td>QLS Total score @ baseline</td>
<td>-</td>
<td>0.95**</td>
</tr>
</tbody>
</table>

(Abbreviations - see Table 1; * p < .05; ** p < .001)
Table 4-3. Predictors of Functional Status (QLS total score)

<table>
<thead>
<tr>
<th>Step</th>
<th>Predictor</th>
<th>R² Change</th>
<th>Beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AES</td>
<td>.743</td>
<td>-.796</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>SAPS Total score</td>
<td>.075</td>
<td>-.281</td>
<td>.025</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step</th>
<th>Predictor</th>
<th>R² Change</th>
<th>Beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AES</td>
<td>.721</td>
<td>-.835</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>CDSS Total score</td>
<td>.094</td>
<td>-.307</td>
<td>.015</td>
</tr>
</tbody>
</table>
Table 4-4. Predictors of Functional Status (QLS total score after exclusion of Intrapsychic Foundations subscale)

**Prediction of Functioning at Baseline**

<table>
<thead>
<tr>
<th>Step</th>
<th>Predictor</th>
<th>$R^2$ Change</th>
<th>Beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AES</td>
<td>.642</td>
<td>-.710</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>SAPS Total score</td>
<td>.140</td>
<td>-.385</td>
<td>.007</td>
</tr>
</tbody>
</table>

**Prediction of Functioning at 6 months**

<table>
<thead>
<tr>
<th>Step</th>
<th>Predictor</th>
<th>$R^2$ Change</th>
<th>Beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AES</td>
<td>.633</td>
<td>-.714</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>CDSS Total score</td>
<td>.096</td>
<td>-.285</td>
<td>.029</td>
</tr>
<tr>
<td>3</td>
<td>SAPS Total score</td>
<td>.080</td>
<td>-.292</td>
<td>.030</td>
</tr>
</tbody>
</table>
Chapter 5

The Determinants of Community Functioning in Schizophrenia: A one-year longitudinal investigation of the role of negative symptoms and cognitive deficits

5.1 Abstract

Impairment in community functioning has long been recognized as a characteristic feature of schizophrenia, despite significant advances in our understanding and treatment of the illness. Recent work has served to highlight the important role for both negative symptoms and cognitive deficits in determining functional outcomes in schizophrenia. Moreover, amongst the constellation of negative symptoms that characterize the illness, motivational deficits have been found to contribute directly to functional impairment, as well as to partially mediate the relationship between cognition and functioning. Most investigations of the determinants of functional outcomes in schizophrenia, however, have focused on the contributions of broad symptom domains, with limited work examining the contribution of discrete symptoms. The aim of the present study was to investigate the concurrent contribution of discrete negative symptoms, cognition, positive symptoms, and depression in the determination of longitudinal community functioning in schizophrenia over the course of one year. We recruited 70 stable adult outpatients with schizophrenia or schizoaffective disorder who underwent clinical, cognitive, and functional evaluations at baseline, and subsequently 6 and 12 months later. Using stepwise multiple regression, followed by confirmation through hierarchical multiple regression with competing predictive models, we found that motivational deficits (i.e., apathy) were the most important predictor of community functioning for individuals with schizophrenia.
Motivational deficits reliably explained between 43% and 58% of the variance in functioning cross-sectionally and longitudinally over the course of one year. Within specific domains of functioning, motivational deficits emerged as most predictive of longitudinal interpersonal and role functioning, and community participation, accounting for between 14% and 54% of the variance in functioning. Cognitive deficits, positive symptoms, and anticipatory pleasure offered limited, and inconsistent, additional predictive value in the determination of community functioning. Overall, these findings suggest that delineation of the psychological and neurobiological underpinnings of motivational deficits is essential as we strive to develop therapeutic interventions to address the functional impairment experienced by individuals with schizophrenia.

5.2 Introduction

Recognition of the functional impairment experienced by individuals with schizophrenia dates back to early descriptions of the phenomenology and course of this illness. Emil Kraepelin, in his classic writings on dementia praecox described in eloquent detail the impairments experienced by these individuals, and noted that adequate functional recovery occurred in approximately 13% of individuals (Kraepelin 1919). Ensuing characterizations of schizophrenia by Eugen Bleuler also highlighted the functional impairment experienced by these patients (Bleuler 1950). With the introduction of antipsychotic medications in the early 1950s came a revolution in the treatment of schizophrenia, with a focus on the treatment of psychotic symptoms and expectations that these new medications would lead to functional recovery and a re-engagement of individuals in the community. Despite significant advances in our understanding and treatment of schizophrenia however, numerous studies examining functional
outcomes continue to find that schizophrenia remains a poor outcome illness (McGlashan 1988; Jobe and Harrow 2005; Mohamed, Rosenheck et al. 2008).

In concert with the extensive work on psychotic symptoms, there continued an undercurrent of research examining negative symptoms in schizophrenia. While the early work by Kraepelin and Bleuler served to highlight the central role for motivational deficits and diminishment of emotional expression in schizophrenia (Kraepelin 1919; Bleuler 1950), seminal work in the 1970s and early 1980s brought forth renewed attention to these negative symptoms and their impact on the course of this illness (Strauss, Carpenter et al. 1974; Crow 1980; Andreasen and Olsen 1982; Wing 1989). Since that time there has been significant progress in our understanding of negative symptoms in schizophrenia, with the current consensus definition of negative symptoms including alogia, affective flattening, asociality, avolition, and anhedonia (Kirkpatrick, Fenton et al. 2006). Further refinements based on factor analyses have revealed the existence of two core subdomains of negative symptoms: diminished expression (including symptoms of alogia and affective flattening); and amotivation (including symptoms of avolition/apathy and asociality) (Foussias and Remington 2010; Messinger, Tremeau et al. 2011). Formal study of emotional experience in schizophrenia has demonstrated that these individuals exhibit an intact capacity to experience pleasure (Cohen and Minor 2010; Llerena, Strauss et al. 2012), with the current thinking around self-reports of non-current emotions suggestive of anhedonia being a reflection of reduced pleasure-seeking behavior, beliefs of low pleasure, and reduced overestimation of past and future pleasure (Strauss and Gold 2012; Strauss 2013).

Beyond these phenomenological advances, negative symptoms have also been consistently linked with functional impairment in schizophrenia across numerous domains, including
occupational functioning, household integration, social functioning, engagement in recreational activities, and quality of life (Ho, Nopoulos et al. 1998; Blanchard, Horan et al. 2005; Malla and Payne 2005; Milev, Ho et al. 2005; Rosenheck, Leslie et al. 2006; Mohamed, Rosenheck et al. 2008; Leifker, Bowie et al. 2009; Hunter and Barry 2012; Rabinowitz, Levine et al. 2012; Verma, Subramaniam et al. 2012). Investigations exploring discrete negative symptoms have revealed that amotivation appears to mediate these relationships with functional outcomes, both cross-sectionally and longitudinally (Sayers, Curran et al. 1996; Kiang, Christensen et al. 2003; Nakagami, Xie et al. 2008; Faerden, Friis et al. 2009; Foussias, Mann et al. 2009; Faerden, Finset et al. 2010; Foussias, Mann et al. 2011; Konstantakopoulos, Ploumpidis et al. 2011; Evensen, Rossberg et al. 2012; Green, Hellemann et al. 2012; Kring, Gur et al. 2013). Anhedonia has shown an inconsistent relationship with functional outcomes (Katsanis, Iacono et al. 1992; Blanchard, Mueser et al. 1998; Herbener, Harrow et al. 2005), as have explorations of the relationships for anticipatory and consummatory facets of the experience of pleasure with functioning (Gard, Kring et al. 2007; Strauss, Wilbur et al. 2011). Similarly, affective flattening and the diminished expression subdomain of negative symptoms have shown a significant relationship in some investigations (Gur, Kohler et al. 2006; Kring, Gur et al. 2013), but not in others (Sayers, Curran et al. 1996; Salem and Kring 1999; Foussias, Mann et al. 2009; Green, Hellemann et al. 2012). Importantly, neurocognitive and social cognitive dysfunction seen in schizophrenia has also been linked to poor functional outcomes (Green, Kern et al. 2000; Green, Kern et al. 2004; Schmidt, Mueller et al. 2011). Recent investigations, however, have demonstrated that the relationship between neurocognition and functioning is at least partially mediated by negative symptom severity (Lipkovich, Deberdt et al. 2009; Ventura, Hellemann et al. 2009; Ojeda, Sanchez et al. 2012). Additional investigations have shown that within negative symptoms it is motivational deficits that appear to be a particularly important mediator of the
relationships with functioning for both neurocognition and social cognition (Nakagami, Xie et al. 2008; Gard, Fisher et al. 2009; Green, Hellemann et al. 2012).

Investigations of the determinants of functioning in schizophrenia have often focused on the contributions of broad domains of symptoms, with limited examinations of the contributions of discrete symptoms. This has been particularly true for negative symptoms, with limited work (described above) that has examined the relative contributions of diminished expression and amotivation subdomains. Further, there have been few studies that have examined the concurrent contribution of such discrete symptoms, along with other important symptom clusters, and their relationship to longitudinal functional outcomes in schizophrenia. Previous pilot work from our group found that in a small sample of individuals with schizophrenia, in the face of positive, depressive, and cognitive symptoms, motivational deficits were the most reliable predictor of functioning both at baseline and 6-month follow-up, with no additional contribution offered by other negative symptoms including diminished expression, anticipatory or consummatory pleasure (Foussias, Mann et al. 2009; Foussias, Mann et al. 2011). Here, we sought to further our understanding of the determinants of longitudinal community functioning in schizophrenia over the course of one year. Specifically, we evaluated the concurrent contribution of discrete negative symptoms, along with other important symptom domains, in predicting cross-sectional and longitudinal functioning in schizophrenia, both for global functioning as well as for discrete domains of community functioning.
5.3 Methods

5.3.1 Participants
Seventy individuals between the ages of 18 and 55 with a DSM-IV diagnosis of Schizophrenia or Schizoaffective Disorder, determined by the Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies (MINI) (Sheehan, Lecrubier et al. 1998), were recruited at the Centre for Addiction and Mental Health, Toronto, Canada. Additional inclusion criteria required that participants were outpatients on stable antipsychotic medication doses for at least 4 weeks. Participants were excluded if they: were incapable to consent to participation; were not fluent in English; met criteria for substance abuse or dependence within the past 3 months; had other DSM-IV Axis I disorders; had a history of neurological disease; had significant akathisia (a rating of > 2 on the Barnes Akathisia Rating Scale Global item (Barnes 1989)), or significant extrapyramidal symptoms (a rating of > 2 on more than 2 items of the Simpson Angus Rating Scale (SARS) (Simpson and Angus 1970)). This study was approved by the institutional research ethics board, and all participants provided written informed consent.

5.3.2 Instruments and Procedures
Following diagnostic assessment and determination of eligibility for study participation, participants underwent evaluations for psychopathology and functional status at baseline, 6 months, and 12 months. Positive and negative symptom severity was evaluated with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982), respectively. Motivational deficit (i.e., apathy) was assessed with the Apathy Evaluation Scale – Clinician version (AES) (Marin, Biedrzycki et al. 1991), an instrument that has been used previously in first-episode and
chronic schizophrenia populations for this purpose (Kiang, Christensen et al. 2003; Foussias, Mann et al. 2009; Faerden, Finset et al. 2010). Anticipatory and consummatory pleasure were assessed with the self-report Temporal Experience of Pleasure Scale (TEPS) (Gard, Gard et al. 2006). Depressive symptoms were evaluated with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington et al. 1990), and cognitive functioning with the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe, Goldberg et al. 2004). Functional status was assessed with the Quality of Life Scale (QLS) (Heinrichs, Hanlon et al. 1984), chosen because of its widespread use as a functional outcome measure in schizophrenia trials (Lieberman, Stroup et al. 2005; Jones, Barnes et al. 2006), and which is a highly rated measure of real-word functioning in schizophrenia (Leifker, Patterson et al. 2011). Participants were evaluated for symptom severity and functional status by independent raters (S.M., I.S., K.M., and G.F.), with the exception of 21 participants at baseline who were evaluated by a single rater. Comparison of cross-sectional correlations between those participants and the remainder of the sample who were evaluated by independent raters did not reveal any significant differences. For all follow-up assessment participants were rated independently for symptom severity and functional status. Inter-rater agreement (i.e., scores within 1 point) was over 80% across all clinical measures.

5.3.3 Analysis

Statistical analysis was performed using SPSS for Mac (SPSS Inc.). SAPS total score consisted of the sum of all items excluding global items, while SANS total score consisted of the sum of all items excluding the attention subscale. The SANS Diminished Expression subdomain was comprised of the SANS Affective Flattening subscale and the poverty of speech item (excluding
inappropriate affect, poverty of content of speech, blocking, response latency, and global items). The BACS composite Z score, calculated based on age and sex normative data, provided a measure of global cognitive function. The mean score of all QLS items excluding the Intrapsychic Foundations subscale, due to overlap in item content between this subscale of the QLS and negative symptom measures, provided a measure of global community functioning. Further, QLS subscale mean scores provided measures of interpersonal functioning (QLS-Interpersonal Relations subscale (QLS-IR)), role functioning (QLS-Instrumental Role subscale (QLS-Role)), and community participation (QLS-Common Objects and Activities subscale (QLS-COA)).

All variables were evaluated for violation of the assumptions of parametric statistical analyses. Variables that were non-normal in their distribution were appropriately square root-transformed (duration of illness, CPZ equivalents, SAPS total score, SANS Diminished Expression score, BACS composite Z-score, QLS-Role score, and QLS-COA score) or log-transformed (CDSS score, and SARS score). Summary statistics were determined for all variables, and chi-square or t tests were used to evaluate differences in demographic and clinical characteristics between study completers and non-completers. Pearson’s correlation coefficients were calculated to examine the bivariate relationships between symptoms and community functioning.

Examinations of the cross-sectional and longitudinal predictors of community functioning at baseline, 6-month, and 12-month follow-up were conducted through stepwise multiple regression, with functioning as the dependent variable, and symptoms as the independent variables. With concerns around the sole use of stepwise multiple regression as an exploratory and atheoretical approach (Tabachnick and Fidell 1996), we also conducted follow-up hierarchical multiple regression analyses evaluating two additional models based on theoretical models of the determinants of functional outcomes in schizophrenia: 1) the addition of cognition
to the hierarchical model prior to entry of predictors emerging from stepwise multiple regression; and 2) the addition of all other symptoms to the hierarchical model, followed by cognition, and finally by predictors emerging from stepwise multiple regression. Examinations of the conditioning index, variance proportions, and variance inflation factor did not reveal evidence of multicollinearity in any of the multiple regression models. Finally, models derived from stepwise and hierarchical multiple regression were compared using the Akaike Information Criterion (AIC) to determine the best fitting model (Akaike 1974).

5.4 Results

5.4.1 Participant demographic and clinical characteristics

A total of 70 participants were recruited and evaluated at baseline as part of this study. Of these, we were able to evaluate 60 participants (85.7%) at 6 months, and 53 participants (75.7%) at 12 months. The mean age of the sample was 37.9 years, with a mean duration of illness of 14.8 years. Of participants assessed at baseline, 75.7% had a diagnosis of schizophrenia, and 24.3% a diagnosis of schizoaffective disorder. Participant demographic and clinical characteristics at baseline are shown in Table 5-1. Comparison of baseline characteristics between those that completed this 12-month longitudinal study and those that were lost to follow-up revealed no significant differences in demographic or clinical characteristics, with the exception of higher mean SAPS total scores in those who did not complete the study (t(68)=2.12, p=.037).
5.4.2 Cross-sectional predictors of functional status in schizophrenia

Our first objective was to examine the cross-sectional determinants of community functioning, and evaluate the stability of these predictors at three separate assessments over the course of 12 months. Initial bivariate correlational analysis revealed that positive symptoms, the diminished expression subdomain of negative symptoms, and cognition exhibited small to moderate relationships with community functioning at baseline, while apathy showed a strong bivariate correlation with community functioning (Table 5-2). Subsequently, we examined the cross-sectional predictors of community functioning using stepwise multiple regression analyses. We found, across three separate assessment periods, that apathy served as the strongest predictor of community functioning at all three assessment periods, accounting for 44% to 48% of the variance in community functioning (Table 5-3). Cognition offered an additional 5% of explained variance only at the 6-month assessment, while positive symptoms accounted for an additional 7% of the variance at the 12-month assessment. Other symptoms including diminished expression, anticipatory and consummatory pleasure, and depression did not offer any additional predictive value at any time point. Moreover, while the predictive value of apathy on community functioning was consistent across time, this was not the case for the contributions of cognition and positive symptoms.

5.4.3 Predictors of longitudinal community functioning in schizophrenia over 1 year

Our second objective was to investigate the determinants of longitudinal community functioning in schizophrenia over the course of 12 months, both for global community functioning, and within the discrete domains of interpersonal functioning, role functioning, and community participation. Bivariate correlational analyses between baseline symptoms and community
functioning at 6-months and 12-months revealed similar relationships for positive symptoms, diminished expression, and apathy as above, but with an emerging additional weak correlation with consummatory pleasure, and an inconsistent relationship with cognition (Table 5-2). Stepwise multiple regression analyses to evaluate the concurrent contributions of symptoms to the prediction of longitudinal functioning revealed that baseline apathy accounted for 58% of the variance in community functioning at 6 months (Table 5-4a), and 44% of the variance in community functioning at 12-month follow-up (Table 5-4b). Other symptoms including diminished expression, anticipatory and consummatory pleasure, positive symptoms, cognition, and depression did not offer any additional predictive value.

Examination of the predictors of longitudinal interpersonal functioning (QLS-IR) revealed that apathy at baseline was the only significant predictor, accounting for 40%, 54%, and 47% of the variance in interpersonal functioning at baseline, 6 months, and 12 months, respectively (Table 5-5). Similar stepwise multiple regression analyses to evaluate the predictors of longitudinal role functioning (QLS-Role) revealed that apathy at baseline was the most important predictor of role functioning, accounting for 14%, 29%, and 15% of the variance in role functioning at baseline, 6 months, and 12 months, respectively (Table 5-6). In addition, positive symptoms emerged as a second important predictor, accounting for 5% and 9% of additional variance explained in role functioning at 6 months and 12 months, respectively. Finally, analyses of the predictors of longitudinal community participation (QLS-COA) revealed that baseline apathy was also the most important predictor of community participation at baseline, 6 months, and 12 months, and accounted for 31%, 24%, and 20% of the variance, respectively (Table 5-7). Cognition at baseline offered additional predictive value for community participation at baseline and 6 months (6% explained variance at each time point), while anticipatory pleasure explained 8% of the variance at 12 months only. Other symptoms including diminished expression, consummatory
pleasure, and depression did not offer any additional predictive value in any domain of community functioning. Importantly, the inclusion of extrapyramidal side effect severity (SARS) did not result in a change in predictors or the amount of explained variance for any of the analyses.

5.4.4 Evaluation of competing models for the prediction of community functioning

Recognizing the concerns around the sole use of stepwise multiple regression for the determination of important predictors of community functioning, we conducted follow-up hierarchical multiple regression analyses at all three time points, examining the contributions of cognition and other symptoms entered into the model prior to apathy. For the cross-sectional prediction of community functioning at baseline, the addition of cognition to the model offered minimal improvement in the model fit compared to apathy alone (AIC = -6.54 vs. -5.98, respectively). To this end, in the final model the standardized beta for cognition was non-significant after accounting for the contribution of apathy (Table 5-8a). Similar hierarchical regression analyses for the cross-sectional prediction of community functioning at 6 and 12 months did not offer improved model fit compared to the models resulting from stepwise multiple regression shown in Table 5-3. Finally, hierarchical multiple regression analyses for the prediction of longitudinal community functioning at 6 months and 12 months, whereby cognition and other symptoms entered the models prior to apathy, did not improve the final model fit compared to the original stepwise regression model with apathy as the sole predictor (Table 5-8b & c).
5.5 Discussion

In the present study we sought to investigate the determinants of longitudinal community functioning in schizophrenia over the course of one year. More specifically, we evaluated the concurrent contribution of discrete negative symptoms, along with other symptom domains, in predicting cross-sectional and longitudinal functioning. We found that motivational deficits (i.e., apathy) are the most reliable predictor of community functioning for individuals with schizophrenia, consistently explaining between 43% and 58% of the variance in functioning cross-sectionally and longitudinally over the course of one year. Other symptoms adding significant predictive value included cognition and positive symptoms, although their individual contributions were relatively small (between 5% and 7%) and inconsistent. Furthermore, other phenomenologically important symptoms including diminished expression, anticipatory and consummatory pleasure, and depression, as well as side effects from antipsychotic medications, did not appear to contribute to community functioning above and beyond the influence of motivational deficits.

In addition to investigating the important contributors to global community functioning in schizophrenia, we evaluated the predictors of longitudinal functioning across discrete domains of community functioning. Across the domains of interpersonal functioning, role functioning, and engagement in the community, baseline motivational deficits reliably emerged as the most important predictor of cross-sectional and longitudinal functioning, accounting for up to 54% of the variance in interpersonal functioning, up to 29% of the variance in role functioning, and up to 31% of the variance in community participation. Similar to findings for global community functioning, positive symptoms and cognition offered some small, though inconsistent, additional predictive value for role functioning and community participation, respectively, as did
anticipatory pleasure for 12-month community participation. In contrast, other symptoms did not significantly contribute towards the prediction of longitudinal functioning beyond that of motivational deficits.

Our finding that motivational deficits serve as the most reliable predictor of cross-sectional and longitudinal community functioning in schizophrenia is in keeping with emerging findings that have supported a significant direct and indirect role for motivation with regards to functional outcomes in schizophrenia (Sayers, Curran et al. 1996; Kiang, Christensen et al. 2003; Nakagami, Xie et al. 2008; Faerden, Friis et al. 2009; Foussias, Mann et al. 2009; Gard, Fisher et al. 2009; Faerden, Finset et al. 2010; Foussias, Mann et al. 2011; Konstantakopoulos, Ploumpidis et al. 2011; Evensen, Rossberg et al. 2012; Green, Hellemann et al. 2012; Kring, Gur et al. 2013). We did not, however, find a consistent and substantial predictive role for cognition, which stands in contrast to previously established findings for the impact of cognitive deficits on functional outcomes in schizophrenia (Green, Kern et al. 2000; Green, Kern et al. 2004).

Further, although the diminished expression subdomain of negative symptoms revealed a moderate bivariate relationship with community functioning, in keeping with some limited previous findings (Gur, Kohler et al. 2006), this did not appear to contribute to the prediction of community functioning beyond the impact of motivational deficits. Similarly, anticipatory pleasure did not reveal a robust relationship with community functioning, with the exception of a contribution towards engagement in the community at 12 months. This stands in contrast to previous work by Gard and colleagues (Gard, Kring et al. 2007), but in line with more recent findings by Strauss and colleagues (Strauss, Wilbur et al. 2011). Not surprisingly, positive symptoms emerged as a somewhat more consistent secondary predictor of longitudinal role functioning impairment, highlighting the importance of vigilant treatment of active psychotic symptoms in this population.
There are some limitations to this study that should be noted. First, a measure of social cognition was not included in this study. Given recent findings for the importance of social cognition in functional outcomes in schizophrenia (Schmidt, Mueller et al. 2011), this would be expected to be an additional important predictor of community functioning. Based on recent structural equation modeling results showing that social cognition influences functional outcomes in schizophrenia along a single pathway through motivational deficits as the final step (Green, Hellemann et al. 2012), however, it is likely that the addition of a measure of social cognition in our study would potentially have improved the amount of variance in community functioning that was explained, without necessarily reducing the overall impact of motivational deficits.

Further, we did not include a measure of defeatist performance beliefs that has emerged as an important psychological factor linked to motivational deficits and negative symptoms more broadly in schizophrenia (Rector, Beck et al. 2005; Grant and Beck 2009). A recent examination of real-world functioning in schizophrenia, however, revealed that while defeatist beliefs appeared to be an important contributor to negative symptoms, it was ultimately negative symptom severity that mediated the relationship between defeatist beliefs and community functioning (Horan, Rassovsky et al. 2010). In light of this, the inclusion of a measure of defeatist beliefs in the present study, while improving our understanding of the contributors of motivational deficits in schizophrenia, would not be expected to substantially impact the predictive value of motivational deficits with regards to longitudinal community functioning.

From a psychometric perspective, there have been concerns around the overlap between measures of motivation from the SANS, which relies primarily on behavioral proxies to evaluate the internal experience of motivation, and functioning as measured by the QLS. For this reason, the AES was used in the present study as it evaluates the loss of motivation within cognitive and emotional spheres, in addition to behavioral considerations (Marin, Biedrzycki et al. 1991).
absence of multicollinearity in our analyses suggests that the AES measures a distinct construct from functioning evaluated using the QLS after exclusion of the intrapsychic foundations subscale.

A further limitation to the present study was that all individuals in the current sample were being treated with antipsychotic medication, which has the potential to cause or worsen some of the motivational and cognitive deficits seen in schizophrenia. We therefore conducted secondary analyses with the inclusion of extrapyramidal side effect severity as an index of the potential cognitive and motivational adverse effects of dopamine antagonism, with no change in predictors for any of our analyses or the strength of their contributions. In addition, the participants that did not complete the longitudinal follow-up in this study exhibited more severe positive symptoms, raising the possibility that in this subgroup it was positive symptoms that may have been a more important predictor of functioning. A secondary analysis in this subgroup (n=17), however, did not reveal a significant relationship between positive symptom severity and community functioning at baseline. Nonetheless, our findings do highlight the important predictive contribution of positive symptoms with regards to longitudinal community functioning in schizophrenia.

Finally, we acknowledge that correlational analyses do not provide information regarding causality, but rather permit the examination of relationships between symptoms and functioning in the context of hypothesized models within which these relationships are interpreted. Based on the current literature in the field, this model considers symptoms of schizophrenia as contributing to the ensuing functional impairment seen in the illness. There are, however, additional possibilities including: 1) functional impairment itself contributing to worsening negative symptoms, and in particular amotivation, potentially through the reinforcement of defeatist
beliefs; and 2) an as yet unidentified third factor causing motivational deficits and functional impairment in schizophrenia.

Negative symptoms in schizophrenia are increasingly recognized for their prominent impact on functional outcomes. Our findings highlight that, within negative symptoms, motivational deficits appear to be the critical determinant of cross-sectional and longitudinal community functioning in schizophrenia, and stand as the most concerning impediment to improved outcomes in this illness. Recent approaches aimed at delineating the neurobiological underpinnings of motivational deficits in schizophrenia have moved us towards an appreciation of the multifaceted nature of motivation and goal-directed behavior (Barch 2005). In conjunction with growing appreciation of psychological factors that may contribute to the loss of motivation, improved understanding of the neurobiology of motivation holds significant promise for the development of therapeutic strategies that will transform outcomes for those with schizophrenia.
Table 5-1. Participant Demographics and Clinical Characteristics (n=70)

<table>
<thead>
<tr>
<th></th>
<th>Mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.9 (10.2)</td>
</tr>
<tr>
<td>Sex (M : F)</td>
<td>49 : 21</td>
</tr>
<tr>
<td>Diagnosis (Schizophrenia : Schizoaffective Disorder)</td>
<td>53 : 17</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>14.8 (11.0)</td>
</tr>
<tr>
<td>Antipsychotic medication class (Atypical : Typical : Both)</td>
<td>59 : 8 : 3</td>
</tr>
<tr>
<td>CPZ equivalents (mg)</td>
<td>460.5 (257.1)</td>
</tr>
<tr>
<td>Positive symptom severity (SAPS)</td>
<td>11.6 (11.8)</td>
</tr>
<tr>
<td>Negative symptom severity (SANS)</td>
<td>24.3 (17.2)</td>
</tr>
<tr>
<td>Diminished expression severity (SANS)</td>
<td>7.5 (7.0)</td>
</tr>
<tr>
<td>Amotivation severity (SANS)</td>
<td>9.5 (7.5)</td>
</tr>
<tr>
<td>Apathy severity (AES)</td>
<td>34.2 (8.1)</td>
</tr>
<tr>
<td>Anticipatory Pleasure score (TEPS)</td>
<td>43.5 (8.4)</td>
</tr>
<tr>
<td>Consummatory Pleasure score (TEPS)</td>
<td>33.9 (7.1)</td>
</tr>
<tr>
<td>Depression score (CDSS)</td>
<td>2.5 (3.0)</td>
</tr>
<tr>
<td>Cognition composite Z-score (BACS)</td>
<td>-1.6 (1.2)</td>
</tr>
<tr>
<td>Extrapyramidal symptom severity (SARS)</td>
<td>0.9 (2.0)</td>
</tr>
<tr>
<td>Community functioning (QLS\textsuperscript{a}) – baseline</td>
<td>3.0 (1.3)</td>
</tr>
<tr>
<td>Interpersonal functioning (QLS-IR) – baseline</td>
<td>3.0 (1.6)</td>
</tr>
<tr>
<td>Measure</td>
<td>Baseline</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Instrumental role functioning (QLS-Role)</td>
<td>2.4 (1.8)</td>
</tr>
<tr>
<td>Community participation (QLS-COA)</td>
<td>3.9 (0.9)</td>
</tr>
<tr>
<td>Community functioning (QLS&lt;sup&gt;a&lt;/sup&gt;) @6-months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.0 (1.3)</td>
</tr>
<tr>
<td>Interpersonal functioning (QLS-IR) @6-months</td>
<td>3.1 (1.6)</td>
</tr>
<tr>
<td>Instrumental role functioning (QLS-Role) @6-months&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Community participation (QLS-COA) @6-months&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Community functioning (QLS&lt;sup&gt;a&lt;/sup&gt;) @12-months&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.1 (1.3)</td>
</tr>
<tr>
<td>Interpersonal functioning (QLS-IR) @12-months&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.1 (1.6)</td>
</tr>
<tr>
<td>Instrumental role functioning (QLS-Role) @12-months&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Community participation (QLS-COA) @12-months&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CPZ – Chlorpromazine; SAPS – Scale for the Assessment of Positive Symptoms; SANS – Scale for the Assessment of Negative Symptoms; AES – Apathy Evaluation Scale; TEPS – Temporal Experience of Pleasure Scale; CDSS – Calgary Depression Scale for Schizophrenia; BACS – Brief Assessment of Cognition in Schizophrenia; SARS – Simpson-Angus Rating Scale; QLS – Quality of Life Scale; QLS-IR – QLS Interpersonal Relations subscale; QLS-Role – QLS Instrumental Role subscale; QLS-COA – QLS Common Objects and Activities subscale. <sup>a</sup> QLS mean score excluding Intrapsychic Foundations subscale; <sup>b</sup> n = 60; <sup>c</sup> n = 53.
Table 5-2. Bivariate correlations between clinical measures at baseline and community functioning over 12 months

<table>
<thead>
<tr>
<th>Baseline Clinical Measures</th>
<th>Community Functioning (QLS) @ baseline</th>
<th>Community Functioning (QLS) @ 6 months</th>
<th>Community Functioning (QLS) @ 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive symptoms (SAPS)</td>
<td>-.27*</td>
<td>-.31*</td>
<td>-.33*</td>
</tr>
<tr>
<td>Diminished expression (SANS)</td>
<td>.29*</td>
<td>-.40**</td>
<td>-.32*</td>
</tr>
<tr>
<td>Apathy (AES)</td>
<td>-.66***</td>
<td>-.76***</td>
<td>-.66***</td>
</tr>
<tr>
<td>Anticipatory Pleasure (TEPS)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Consummatory Pleasure (TEPS)</td>
<td>ns</td>
<td>.26*</td>
<td>.24*</td>
</tr>
<tr>
<td>Depression (CDSS)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Cognition composite Z-score (BACS)</td>
<td>.36**</td>
<td>.36**</td>
<td>ns</td>
</tr>
<tr>
<td>Extrapyramidal symptom severity (SARS)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Community functioning (QLS) @ baseline</td>
<td>-</td>
<td>.93***</td>
<td>.83***</td>
</tr>
<tr>
<td>Community functioning (QLS) @ 6 months</td>
<td>-</td>
<td>-</td>
<td>.91***</td>
</tr>
</tbody>
</table>

Abbreviations: see Table 1. ns. not significant; * p<.05; ** p<.01; *** p<.001; a p=.085.
Table 5-3. Cross-sectional predictors of community functioning

<table>
<thead>
<tr>
<th></th>
<th>R² change</th>
<th>Beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Community functioning at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.441</td>
<td>-.664</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>B Community functioning at 6-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.484</td>
<td>-.586</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2. Cognition</td>
<td>.045</td>
<td>.238</td>
<td>.024</td>
</tr>
<tr>
<td><strong>C Community functioning at 12-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.435</td>
<td>-.639</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2. Positive symptoms</td>
<td>.071</td>
<td>-.267</td>
<td>.010</td>
</tr>
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Table 5-4. Baseline predictors of longitudinal community functioning

<table>
<thead>
<tr>
<th></th>
<th>R² change</th>
<th>Beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Community functioning at 6-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.580</td>
<td>-.761</td>
<td>&lt;.001</td>
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<tr>
<td><strong>B Community functioning at 12-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.430</td>
<td>-.656</td>
<td>&lt;.001</td>
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Table 5-5. Baseline predictors of longitudinal interpersonal functioning (QLS-IR)

<table>
<thead>
<tr>
<th></th>
<th>R^2 change</th>
<th>Beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Interpersonal functioning at baseline</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.402</td>
<td>-.634</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>B Interpersonal functioning at 6-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.537</td>
<td>-.733</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>C Interpersonal functioning at 12-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.469</td>
<td>-.685</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Table 5-6. Baseline predictors of longitudinal role functioning (QLS-Role)

<table>
<thead>
<tr>
<th></th>
<th>R² change</th>
<th>Beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Role functioning at baseline</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.144</td>
<td>-.380</td>
<td>.001</td>
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<tr>
<td><strong>B Role functioning at 6-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.289</td>
<td>-.475</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2. Positive symptoms</td>
<td>.050</td>
<td>-.232</td>
<td>.043</td>
</tr>
<tr>
<td><strong>C Role functioning at 12-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.146</td>
<td>-.314</td>
<td>.017</td>
</tr>
<tr>
<td>2. Positive symptoms</td>
<td>.091</td>
<td>-.309</td>
<td>.018</td>
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Table 5-7. Baseline predictors of longitudinal community participation (QLS-COA)

<table>
<thead>
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<th></th>
<th>R² change</th>
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<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Community participation at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.308</td>
<td>-.468</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2. Cognition</td>
<td>.059</td>
<td>.258</td>
<td>.015</td>
</tr>
<tr>
<td><strong>B Community participation at 6-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.244</td>
<td>-.406</td>
<td>.001</td>
</tr>
<tr>
<td>2. Cognition</td>
<td>.061</td>
<td>.263</td>
<td>.029</td>
</tr>
<tr>
<td><strong>C Community participation at 12-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.203</td>
<td>-.404</td>
<td>.002</td>
</tr>
<tr>
<td>2. Anticipatory pleasure</td>
<td>.080</td>
<td>.287</td>
<td>.022</td>
</tr>
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</table>
Table 5-8. Comparison of hierarchical regression models for prediction of longitudinal community functioning

<table>
<thead>
<tr>
<th></th>
<th>$R^2$ change</th>
<th>Beta</th>
<th>p</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Community functioning at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
<td></td>
<td>-5.98</td>
</tr>
<tr>
<td>1. Apathy</td>
<td>.441***</td>
<td>-.664</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
<td>-6.54</td>
</tr>
<tr>
<td>1. Cognition</td>
<td>.129**</td>
<td>.151</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>2. Apathy</td>
<td>.332***</td>
<td>-.613</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Model 3:</td>
<td></td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>1. All other symptoms</td>
<td>.174*</td>
<td>-</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>2. Cognition</td>
<td>.097**</td>
<td>.171</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>3. Apathy</td>
<td>.214***</td>
<td>-.560</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td><strong>B Community functioning at 6-month follow-up</strong></td>
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<tr>
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1. Apathy  
   Model 2:  
   1. Cognition  
   2. Apathy  
   Model 3:  
   1. All other symptoms  
   2. Cognition  
   3. Apathy  

C Community functioning at 12-month follow-up

Model 1:  
1. Apathy  

Model 2:  
1. Cognition  
2. Apathy
Model 3:  

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Abbreviations: AIC – Akaike Information Criterion; ns. not significant. * p<.05; ** p<.01; *** p<.001
Chapter 6

6 Motivated to do well: Exploration of the relationships between motivation, effort, and cognitive test performance in schizophrenia

6.1 Abstract

The relationship between negative symptoms, and specifically motivational deficits, and cognitive dysfunction in schizophrenia has raised questions regarding cognitive impairments in schizophrenia and their relationship to a lack of motivation to do well on cognitive testing. Findings to date have suggested some broad impact of motivational deficits on cognitive performance, although with inconsistent findings from formal examinations of effort using performance validity measures. The aim of this study was to examine the relationships between motivation, effort exerted during cognitive testing, and cognitive performance in schizophrenia. Sixty-nine outpatients with schizophrenia or schizoaffective disorder were evaluated for psychopathology, severity of motivational deficits, effort exerted during cognitive testing, and cognitive performance. Motivation in schizophrenia was significantly related to cognitive performance, with this relationship most robust in terms of verbal fluency. Moreover, effort exerted during cognitive testing was related to both motivational deficits and cognitive performance across several domains. However, scores on performance validity measures appeared to be influenced by cognitive deficits seen in schizophrenia, and thus not measuring motivation alone. Examining profiles of individuals exerting normal or low effort during testing, differences appeared to be determined by worse cognitive performance in the low-effort group, with no differences in motivation. Overall, these findings indicate a differential relationship...
between motivation and cognitive domains, with a particular relationship with verbal fluency. Our findings using a performance validity measure suggest that, although believed to be insensitive to cognitive impairment, performance on such tests is influenced by cognitive impairment in schizophrenia, highlighting the need for alternative strategies for evaluating mental effort in this illness.

6.2 Introduction

Motivational deficits have long been recognized as a central feature of the phenomenology of schizophrenia, dating back to some of the earliest descriptions of this illness by Kraepelin and Bleuler (Kraepelin 1919; Bleuler 1950). This lack of motivation has served as one of the negative symptoms of schizophrenia in contemporary definitions (Andreasen 1982; Kirkpatrick, Fenton et al. 2006). Additionally, recent work has identified motivational deficits as one of the two core subdomains of negative symptoms in schizophrenia (Foussias and Remington 2010; Messinger, Tremeau et al. 2011). Moreover, motivational deficits have been shown to play important roles in predicting cross-sectional and longitudinal functional outcomes in both first-episode and chronic schizophrenia populations (Sayers, Curran et al. 1996; Kiang, Christensen et al. 2003; Faerden, Friis et al. 2009; Foussias, Mann et al. 2009; Faerden, Finset et al. 2010; Foussias, Mann et al. 2011; Konstantakopoulos, Ploumpidis et al. 2011; Evensen, Rossberg et al. 2012). Beyond these direct relationships, recent work examining the interaction between negative symptoms and cognitive deficits, and their respective relationships with functional outcomes in schizophrenia have revealed that negative symptoms also appear to mediate the relationship between cognition and functioning (Ventura, Hellemann et al. 2009). Further work in this area by several groups has served to highlight that motivational deficits appear to drive
these indirect relationships, partially mediating the relationship between cognition and functional outcomes, with significant roles in both neurocognition and social cognition (Nakagami, Xie et al. 2008; Gard, Fisher et al. 2009; Green, Hellemann et al. 2012).

Negative symptoms, and motivational deficits in particular, have also exhibited direct relationships with cognitive dysfunction seen in schizophrenia. Numerous cross-sectional investigations have found significant correlations between the severity of negative symptoms and neurocognitive deficits in schizophrenia (e.g., (Cornblatt, Lenzenweger et al. 1985; Green and Walker 1985; Liddle 1987; Andreasen, Flaum et al. 1990; Stolar, Berenbaum et al. 1994; Zakzanis 1998)). Extensive reviews of this body of research have concluded that while some moderate relationship exists, with approximately 10% of shared variance, they nevertheless represent separate domains of psychopathology (Addington 2000; Harvey, Koren et al. 2006). Longitudinal investigations to further disentangle the nature of their relationship have revealed, though again not consistently, that negative symptoms and neurocognitive deficits appear to change independently over time, further reinforcing the conclusion that they represent separate, yet somewhat related, symptom domains (Harvey, Lombardi et al. 1996; Addington, Addington et al. 1997; Green, Marshall et al. 1997; Hughes, Kumari et al. 2003; Bell and Mishara 2006). A focused longitudinal examination of the relationship between motivational deficits and neurocognition revealed similar findings, with these two domains changing independently over time (Nakagami, Hoe et al. 2010). Finally, a cross-sectional examination of the relationship between social cognition, neurocognition, and negative symptoms found that social cognition was much more closely related to neurocognition, with only a modest relationship with negative symptoms (Sergi, Rassovsky et al. 2007).
There has been growing recognition of the potential impact of motivation on cognitive test performance, with questions as to whether some of the cognitive impairment seen in schizophrenia is driven by a lack of motivation to do well on cognitive tasks (Barch 2005). Early work by Schmand et al. (1994) explored this question within a computational-energetic framework, with the view that computational mechanisms relate to the information processing necessary to carry out cognitive tasks, while energetic mechanisms relate to energizing or motivational aspects of information processing such as arousal and mental effort (Schmand, Kuipers et al. 1994). In their investigation examining performance of psychotic and non-psychotic disorder psychiatric patients on a simple reaction task they found that the psychotic group exhibited energetic deficits, but without computational impairment, and further, that those with energetic deficits performed significantly worse on attention, vigilance, and verbal memory tasks. Based on their findings, they suggested that cognitive dysfunction in psychotic disorders was related more to deficits in energetic (i.e., motivation) rather than computational mechanisms (Schmand, Kuipers et al. 1994). In keeping with this, motivational deficits measured clinically have shown significant relationships with cognitive performance, and specifically with verbal fluency, working memory, attention and set-shifting, and verbal learning and memory (Addington and Addington 1999; Roth, Flashman et al. 2004; Nakagami, Xie et al. 2008; Faerden, Vaskinn et al. 2009; Gard, Fisher et al. 2009; Konstantakopoulos, Ploumpidis et al. 2011). Further, use of monetary incentives to evaluate the impact of motivation on cognitive task performance has revealed that on some cognitive tasks, such as the Wisconsin Card Sorting Task (Heaton 1981), the Span of Apprehension (Asarnow and Nuechterlein 1987), and facial emotion recognition tasks (Kerr and Neale 1993), performance can be improved through the use of such incentives (Summerfelt, Alphs et al. 1991; Kern, Green et al. 1995; Penn and Combs 2000). Importantly, this has not been consistent across all studies (Green, Ganzell et al. 1990),
highlighting that motivational deficits may differentially impact functioning across cognitive domains.

An alternative approach to investigate the impact of motivational deficits on cognitive test performance has been to assess the degree of effort individuals exert during cognitive testing. This has routinely been accomplished in neuropsychological examinations through the use of performance validity tests (PVTs). Such PVTs often employ forced-choice tasks whereby individuals are presented a series of verbal or visual stimuli, followed by presentation of pairs of stimuli from which they must identify the one that was previously presented (Bianchini, Mathias et al. 2001). PVTs have mostly been employed in the context of litigation and compensation assessments to identify malingering. Their use, however, has not been without controversy, given the absence of a “gold standard” for cognitive effort, and their validation based on simulation or known-group designs, both of which present their own limitations (Bianchini, Mathias et al. 2001; Bigler 2012). Nonetheless, PVTs are seen as an important component of neuropsychological evaluations to evaluate whether participants are providing sufficient effort during neuropsychological testing (Sharland and Gfeller 2007; McCarter, Walton et al. 2009; Fox 2011). Moreover, PVTs have been increasingly used for the assessment of effort in non-litigation settings, including in children, adolescents, healthy undergraduate university student volunteers, and in patients with neurological conditions including epilepsy, Alzheimer’s disease, and traumatic brain injury patients (Merten, Bossink et al. 2007; Locke, Smigielski et al. 2008; Axelrod and Schutte 2011; Kirk, Harris et al. 2011; An, Zakzanis et al. 2012; Brooks, Sherman et al. 2012; Wisdom, Brown et al. 2012).

Across psychiatric populations, investigations using PVTs have revealed that depression and anxiety disorders do not appear to impact PVT scores (reviewed in (Goldberg, Back-Madruga et
al. 2007)). In schizophrenia, however, there have been mixed findings. Early studies using PVTs in schizophrenia populations identified 13% to 27% of individuals as exerting insufficient effort (i.e., failing the PVT) (Back, Boone et al. 1996; Goldberg, Back-Madruga et al. 2007). Ensuing work by Egeland et al. (2003), comparing individuals with schizophrenia, depression, and healthy controls, using the Victoria Symptom Validity Test (VSVT) to assess effort, found that 5% of individuals with schizophrenia exerted insufficient effort, which was not significantly different from other groups where no individuals exerted insufficient effort (Egeland, Sundet et al. 2003). An investigation by Duncan (2005) in individuals with psychotic disorders using the Test of Memory Malingering (TOMM; (Tombaugh 1996)), one of the most frequently used PVTs (Sharland and Gfeller 2007; McCarter, Walton et al. 2009), found that 8% of participants exerted insufficient effort, and that this appeared to be driven by concentration impairments (Duncan 2005).

A subsequent examination by Gorrisen et al. (2005) explored the impact of effort on cognitive test performance in individuals with schizophrenia compared to non-schizophrenia psychiatric controls (including subjects with depression, anxiety, personality disorders, eating disorders, and adjustment disorders), neurological controls (including participants with traumatic brain injury, neurodegenerative disorders, vascular disorders, brain tumors, epilepsy, and multiple sclerosis), as well as healthy control participants (Gorissen, Sanz et al. 2005). In their study, using another common PVT, the Word Memory Test (WMT), they found the prevalence of insufficient effort to be 72% in the schizophrenia group, compared to 25% in the psychiatric control group, 10% in the neurological control group, and 0% in the healthy control group. Effort accounted for between 14% and 35% of the variance in cognitive test scores, and was significantly correlated with negative symptom severity in the schizophrenia group (Gorissen, Sanz et al. 2005).
A more recent study, however, by Avery et al. (2009) also used the WMT to assess effort in schizophrenia participants, and found much better performance in their sample, with average scores on the WMT comparable to the psychiatric control group in Gorrisen et al. (2005) (Avery, Startup et al. 2009). Interestingly, while effort correlated with total negative symptoms, this appeared to be driven by relationships with alogia and anhedonia, but with no significant relationship with avolition. Finally, Schroeder and Marshall (2011) examined performance across seven PVTs in psychotic and non-psychotic psychiatric populations, and found that insufficient effort determined by failure on a single PVT was equally prevalent in psychotic and non-psychotic groups (19% and 17%, respectively) (Schroeder and Marshall 2011). Using more stringent criteria (i.e., requiring failure on two PVTs) they found reduced, and non-significantly different, prevalence rates of insufficient effort in psychotic and non-psychotic participant groups (7% and 5%, respectively).

Another strategy to evaluate mental effort employed by Granholm and colleagues (2007) examined pupillary responses during cognitive testing to index mental effort, with greater pupillary dilation being indicative of increased mental effort (Granholm, Verney et al. 2007). In comparison to healthy participants, there existed two groups of schizophrenia participants, one exerting normal mental effort and one exerting reduced mental effort during cognitive testing, with pupillary responses being significantly correlated with negative symptom severity. While individuals in both groups showed equal impairment in cognitive task performance, those in the low effort group had more severe negative symptoms. More recently, work by Gold and colleagues (2013) investigating effort-cost computations in schizophrenia found that willingness to exert effort during a decision-making task was correlated with better global cognitive performance, and in particular with processing speed, verbal and visual memory, and reasoning/problem solving domains (Gold, Strauss et al. 2013).
Given the relationships between motivational and cognitive deficits with functional outcomes in schizophrenia, disentangling the impact of motivation on cognitive functioning remains essential as we strive to identify critical treatment targets that will serve to improve functional outcomes in this illness. To this end, the aim of this study was to examine the relationships between motivation, effort exerted on cognitive testing as determined by a widely adopted PVT, and cognitive functioning in schizophrenia. Specifically, we sought to determine the relationship between cognition and clinical measures of motivation routinely employed in schizophrenia research, both for global cognitive performance and across specific cognitive subdomains. We also sought to clarify the relationship of effort as measured by the TOMM with motivation and cognition both as a continuous and dichotomous construct. This was driven in large part by the recognition that classification of effort as sufficient or insufficient, while useful for forensic evaluations, may not accurately capture the variations in effort that individuals with schizophrenia may exhibit when undertaking cognitive testing. Finally, we investigated the validity of the TOMM as an index of effort in schizophrenia, specifically examining whether poor performance on effort testing was predicted by a lack of motivation or cognitive dysfunction in the illness.

6.3 Methods

6.3.1 Participants

Individuals between the ages of 18 and 55 with a DSM-IV diagnosis of Schizophrenia or Schizoaffective Disorder, determined by the Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies (MINI) (Sheehan, Lecrubier et al. 1998), were recruited at the Centre for Addiction and Mental Health, Toronto, Canada. All participants were outpatients on stable doses of antipsychotic medications for at least 4 weeks. Participants were
excluded from the study if they: met criteria for substance abuse or dependence within the past 3 months, or other DSM-IV Axis I disorders; had a history of neurological disease; were experiencing significant akathisia (a rating of > 2 on the Barnes Akathisia Rating Scale Global item (Barnes 1989)), or significant extrapyramidal symptoms (a rating of > 2 on more than 2 items of the Simpson Angus Rating Scale (Simpson and Angus 1970)).

6.3.2 Instruments and Procedures
Positive and negative symptom severity was evaluated with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982), respectively. Amotivation was assessed using the Apathy Evaluation Scale – Clinician version (AES) (Marin, Biedrzycki et al. 1991), as well as the Intrinsic Motivation factor derived from the Quality of Life Scale (Heinrichs, Hanlon et al. 1984; Nakagami, Xie et al. 2008). Depressive symptoms were evaluated with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington et al. 1990). Effort exerted during cognitive testing was evaluated using the TOMM (Tombaugh 1996). Cognitive functioning was measured with the Brief Assessment of Cognition in Schizophrenia (BACS), which has shown excellent psychometric properties in comparison with much more extensive batteries (Keefe, Goldberg et al. 2004; Hill, Sweeney et al. 2008), and allows for the determination of a composite cognitive functioning score, as well as scores for individual domains of Verbal Memory (List Learning), Working Memory (Digit Sequencing Task), Motor Speed (Token Motor Task), Verbal Fluency (Category Instances, and Letter Fluency), Attention/Processing Speed (Symbol Coding), and Executive Function (Tower of London) (Keefe, Goldberg et al. 2004). Following diagnostic assessment, participants were evaluated in a single study visit by trained raters (S.M.,
I.S., K.M., or G.F.), whose interrater agreement was over 80%. This study was approved by the local research ethics board, and all participants provided informed consent.

6.3.3 Analysis

Statistical analysis was performed using SPSS for Mac (SPSS Inc.). All variables were evaluated for violations of the assumptions of parametric statistical analyses. Variables that were non-normal in their distribution were appropriately square root or log-transformed. Pearson’s correlation coefficients were calculated to examine the bivariate relationships between motivation and cognitive performance (both for global and subcomponents of cognition), as well as relationships with other symptoms. SAPS total score consisted of the sum of all items excluding global items, while SANS total score consisted of the sum of all items excluding the attention subscale. Further, negative symptoms were separated into their 2 core subdomains: Diminished Expression and Amotivation (reviewed in (Foussias and Remington 2010)). The SANS Diminished Expression subdomain was comprised of the SANS Affective Flattening subscale and the Poverty of Speech item (excluding inappropriate affect, poverty of content of speech, blocking, response latency, and global items). The SANS Amotivation subdomain was comprised of the SANS Avolition-Apathy and Anhedonia-Asociality subscales (excluding global items). The Intrinsic Motivation score consisted of the mean score for QLS items Purpose, Motivation, and Curiosity. The BACS subtest and composite scores were transformed into standardized Z-scores based on age and sex normative data. Chlorpromazine (CPZ) equivalents for antipsychotic medication were calculated based on Andreasen et al. (2010), and for those antipsychotics not listed there, based on Kane et al. (1998), Kroken et al. (2009), and Buchanan et al. (2010) (Kane, Aguglia et al. 1998; Kroken, Johnsen et al. 2009; Andreasen, Pressler et al.
Given the number of bivariate correlations examined between measures of motivation and BACS subtests (18 correlations), the Bonferroni-Holm procedure was used to correct for multiple statistical tests (Holm 1979).

For the examination of relationships between cognitive functioning and scores on the PVT (TOMM), we conducted statistical analysis based on TOMM Trial 1 (TOMM1) scores as both a continuous measure of effort, as well as a dichotomous classification, with TOMM1 scores < 41 being indicative of failure on the TOMM (i.e., < 82% correct), in keeping with the previous findings for the TOMM showing that this cut-off exhibits high levels of sensitivity and specificity in mixed psychiatric populations, and may serve as a better measure of test validity than the original scoring procedure involving the use of a second and retention trial (Hilsabeck, Gordon et al. 2011; Denning 2012). Pearson’s correlation coefficients were calculated to examine bivariate relationships between effort, motivation, and cognitive test performance, along with Bonferroni-Holm correction for correlations between effort and BACS subtests (6 correlations). Additionally, in order to evaluate the contributions of motivation and cognitive function to effort test performance, stepwise multiple regression analyses were conducted for global cognitive function and for subdomains of cognition with significant bivariate correlations with effort. Finally, chi-squared and $t$ tests, as appropriate, were used to evaluate differences in demographics, psychopathology, and cognitive test performance between subjects that passed and failed the TOMM (Normal Effort (NE) and Low Effort (LE) groups, respectively).
6.4 Results

6.4.1 Participant demographics and clinical characteristics

A total of 69 individuals were recruited and evaluated as part of this study. The mean age of the sample was 38.0 years, with a mean duration of illness of 14.9 years. In this sample 77% had a diagnosis of schizophrenia, with the remainder a diagnosis of schizoaffective disorder, and 70% were male. The mean daily chlorpromazine equivalent dose was 458.2 mg. Participant demographic and clinical characteristics are shown in Table 6-1.

6.4.2 The relationship between motivation and cognitive performance in schizophrenia

Examination of the relationship between motivation and cognitive performance revealed several significant correlations (Table 6-2). Global cognition was significantly correlated with Intrinsic Motivation (r = .35, p=.004), and inversely correlated with severity of amotivation as measured by the AES and SANS Amotivation subdomain (r = -.33, p = .006, and r = -.42, p < .001, respectively). Further examination of the relationship between motivation and discrete domains of cognition revealed significant relationships between Intrinsic Motivation and: verbal memory (r = .27, p = .023); verbal fluency (r = .42, p < .001); and a trend towards significant relationship with processing speed (r = .24, p = .050). Apathy severity also showed significant relationships with discrete domains of cognition, with AES score being correlated with verbal fluency (r = -.40, p = .001). SANS Amotivation severity also revealed significant relationships with verbal memory (r = -.24, p = .043), working memory (r = -.33, p = .006), and verbal fluency (r = -.50, p < .001), and at a trend level with attention/processing speed (r = -.24, p = .051). After controlling for multiple tests of significance for correlations between measures of motivation and
BACS subtests only the relationships between Intrinsic Motivation, AES, and SANS Amotivation with Verbal Fluency remained significant. Of note, extrapyramidal symptom severity (SARS) was not correlated with any measure of motivation or cognition with the exception of attention/processing speed \((r = -.31, p = .009)\). Partial correlation after controlling for SARS severity led to the trend-level relationship between motivation and attention/processing speed being non-significant.

6.4.3 The relationships between effort test performance, motivation, and cognition in schizophrenia

In order to evaluate the ability of effort test performance to capture amotivation as it pertains to cognitive test performance, we first examined bivariate correlations between PVT scores (i.e., TOMM1 scores), measures of motivation, and cognitive test performance (Table 6-3). This revealed that PVT scores were significantly correlated with Intrinsic Motivation \((r = .370, p = .002)\), AES-C score \((r = - .291, p = .015)\), and SANS Amotivation \((r = - .314, p = .009)\). Importantly, PVT scores were not correlated with other measures of psychopathology. With regards to cognition, PVT scores were significantly correlated with global cognition \((r = - .387, p = .001)\), as well as with Verbal Fluency \((r = - .409, p < .001)\), Executive Function \((r = - .343, p = .004)\), Attention/Processing Speed \((r = - .301, p = .012)\), and Working Memory \((r = - .264, p = .028)\). After applying Bonferroni-Holm correction only the relationship with Working Memory was no longer significant. Importantly, SARS severity was not correlated with PVT score.

Subsequently, we conducted stepwise multiple regression analyses to further investigate the validity of the TOMM, and determine the contributions of motivation and cognition in predicting PVT scores. When examining global cognition, overall cognitive test performance was the
strongest predictor of PVT score, accounting for 15% of the variance, with Intrinsic Motivation accounting for an additional 6% of variance (Table 6-4a). With regards to specific cognitive subtests with significant bivariate correlations to PVT scores: Verbal Fluency accounted for 17% of the variance in PVT scores, with Intrinsic Motivation accounting for an additional 5% of variance (Table 6-4b); whereas for Executive Function and Attention/Processing Speed, Intrinsic Motivation was the most significant predictor of PVT score accounting for 14% of the variance in both cases, with Executive Function accounting for an additional 7% of variance, and Attention/Processing Speed not being a significant predictor of PVT score after accounting for motivation (Table 6-4c & 6-4d).

In addition to examining effort as a continuous measure, we also conducted analyses of group differences after categorizing participants into NE and LE groups. Of the entire sample, 8 participants (11.6%) comprised the LE group, with 61 participants (88.4%) comprising the NE group. Group comparisons revealed significant differences on measures of global cognitive performance (t(67) = 2.53, p = .014) and SANS Diminished Expression (t(67) = 2.49, p = .015). However, there were no significant differences between NE and LE groups on measures of motivation, age, duration of illness, or other measures of psychopathology or antipsychotic side effect ratings (Table 6-5). We further explored group differences across BACS subtests, which revealed significant differences between NE and LE groups in Attention/Processing Speed (t(67)=2.59, p = .012) and Executive Function (t(8)=2.52, p = .037), as well as a trend for Verbal Fluency (t(67)=1.73, p = .088) (Table 6-6). These findings for both global cognitive function and specific subdomains of cognition are shown graphically in Figure 6-1.
6.5 Discussion

In recognition of the need for further delineation of the relationship between motivation and cognitive functioning, as well as recent discrepant findings around the role of effort and cognitive test performance, we sought to investigate the relationships between motivation, effort exerted during cognitive testing, and cognitive test performance in schizophrenia. In a sample of 69 adult participants with schizophrenia or schizoaffective disorder, we found that motivation was moderately and significantly correlated with global cognitive performance, and moreover, that this relationship was driven primarily by a moderate to strong relationship with verbal fluency. This is in keeping with previous literature indicating a relationship between negative symptoms, and specifically motivational deficits, and verbal fluency (Addington and Addington 1999; Roth, Flashman et al. 2004; Nakagami, Xie et al. 2008; Faerden, Vaskinn et al. 2009; Gard, Fisher et al. 2009; Konstantakopoulos, Ploumpidis et al. 2011). This previous work has also shown motivational deficits to be related to verbal memory and working memory, which was also found in the current investigation, although these relationships did not survive corrected significance thresholds. Overall these findings serve to highlight the differential relationship for motivation across cognitive domains, with some areas being more correlated with motivational deficits, and some areas relatively unrelated. Our finding of a particular relationship between motivation and verbal fluency raises the possibility that, in schizophrenia, performance in this domain of cognitive testing may be particularly sensitive to the individual’s level of motivation.

We subsequently examined the relationship between effort exerted during cognitive testing, clinical measures of motivation, and cognitive performance. Using the TOMM, a widely used PVT to index effort, we found that performance was moderately correlated with clinical measures of motivation and with global cognitive performance. With regards to cognition, this
relationship appeared to be driven by significant relationships with verbal fluency, executive function, and attention/processing speed. To determine whether PVT scores were due to lack of motivation or cognitive impairment, we conducted a series of multiple regression analyses. Through these, we found that global cognition and verbal fluency contributed considerably more to the prediction of PVT scores than lack of motivation. However, lack of motivation appeared to be a more important predictor of PVT score for tests of executive function and attention/processing speed. Finally, we investigated differences in clinical and cognitive symptoms between those individuals exerting normal and low effort during cognitive testing. We found that individuals exerting low effort during cognitive testing (approximately 12% of our sample) had significantly more expressive impairment (i.e., affective flattening and poverty of speech), although with no significant difference in motivation. In addition, they appeared to have more severe cognitive impairments, driven by worse performance on tests of executive function and attention/processing speed.

The prevalence of low effort using the TOMM in the current study is consistent with findings described earlier using both this and other PVTs in schizophrenia. However, our findings also suggest that performance on at least the TOMM, while somewhat related to motivation measured through clinical rating instruments, is also related to cognitive deficits seen in schizophrenia. Moreover, those individuals classified as exhibiting low effort did not evince more severe motivational deficits, but rather appeared to be characterized by more severe cognitive impairment. These results are in keeping with the findings of several others who have found PVT performance to be related to cognitive impairments and other negative symptoms aside from amotivation (Duncan 2005; Avery, Startup et al. 2009), although in contrast to the findings by Gorissen et al. (2003) (Gorissen, Sanz et al. 2005). These discrepancies between studies have raised questions around the differential cognitive demands among different PVTs. Some initial
efforts to address this have examined performance on PVTs including the WMT and TOMM in the presence and absence of additional cognitive demands. Through the use of simple and complex distraction tasks, performance on the WMT has been shown to be substantially influenced by cognitive load, with reduced performance in the face of distractors, whereas TOMM performance appears to be unaffected by such increased cognitive load (Batt, Shores et al. 2008; Schroeder and Marshall 2011). While the above studies have highlighted that the WMT, initially thought to solely index effort and be insensitive to cognitive impairment, is in fact impacted by cognitive capacity, our findings raise the same concerns for the TOMM, and suggest that performance on this PVT also appears to be influenced by cognitive capacity in individuals with schizophrenia.

There are some limitations to the current study that should be noted. First, we did not include a healthy or non-psychotic psychiatric comparison population with which to compare our findings. This limits our ability to draw conclusions beyond schizophrenia, and does not address the potential impact of a chronic psychiatric illness on the willingness to exert effort during cognitive testing. However, previously published studies using the TOMM suggests that those individuals in our study exhibiting normal effort had equivalent mean scores to healthy controls, traumatic brain injury subjects, and depressed subjects in other studies, while those exhibiting low effort had substantially reduced mean scores (Tombaugh 1996; Rees, Tombaugh et al. 2001). There have also been concerns with the use of cut-off scores for categorizing individuals as exhibiting low effort, as well as concerns around false positives and negatives with PVT use. Recognizing the concerns around the use of cut-off scores for dichotomizing participants into normal and low-effort groups and the potential for inappropriate classifications, we opted to utilize both categorical and continuous analytic strategies when examining the relationships between effort and cognitive performance, which we believe offers a more balanced and
conservative approach to examining these relationships. Importantly, poor performance on the TOMM in our sample was not viewed as suggestive of feigned cognitive impairment by those participants, as is the case in forensic samples, as there were no advantages for performing poorly. In addition, although PVTs, including the TOMM, have frequently been used for the examination of effort during cognitive testing, the establishment of the construct validity of these instruments has been limited by the absence of a gold standard. This limitation is addressed in part in the present study whereby we examine the relationship between TOMM performance and clinical measures of motivation, although a specific measure of mental effort was not included in the present study. Further, the use of only trial 1 of the TOMM in the present study, although having been found to exhibit good sensitivity and specificity in relation to performance on trial 2 and the retention trial of the TOMM, represents an abbreviated form of this PVT. In addition, the use of multiple PVTs, rather than a single PVT, within the context of a neuropsychological examination would incrementally add validity to any conclusions regarding effort per se.

Importantly, all individuals in the current sample were being treated with antipsychotic medication, which has the potential to cause or worsen some of the motivational and cognitive deficits seen in schizophrenia. In light of these we examined extrapyramidal side effect severity in these subjects as an index of the potential cognitive and motivational adverse effects of dopamine antagonism. Extrapyramidal symptom severity was not correlated with clinical measures of motivation, scores on the PVT, or cognition with the exception of attention/processing speed. However, after controlling for SARS severity, the only effect was the reduction of a trend-level relationship with motivation to a non-significant one. Further, there was no significant difference in antipsychotic side effect severity, or for that matter in antipsychotic dose equivalents, between those characterized as exerting normal versus low effort during cognitive testing. An additional limitation relates to the use of BACS subtests as
measures of domains of cognition, with the limited number of tests for each domain being below the recommended number for adequately evaluating discrete constructs (Kenny, Kashy et al. 1988). Finally, while the use of correlational analysis is valuable to examine interrelationships between symptoms, it does not provide conclusions about causation. The relationships seen in the present study, however, are interpreted in the context of a potential causal pathway whereby change in motivation leads to change in cognitive performance, in line with previous findings of monetary incentives leading to improved cognitive performance.

Overall, the findings of the present examination, in conjunction with previous work in this area, serve to highlight the complexity of the relationship between motivation and cognitive performance, whereby motivation is differentially related to cognitive domains, with some being more closely linked with amotivation. Moreover, the moderate relationship between PVT performance and clinical measures of motivation raises questions about whether the TOMM measures effort towards cognitive testing in schizophrenia, and suggests that other strategies to index mental effort may be preferable. As we move towards greater understanding of the impact of cognitive and motivational deficits on the functional outcomes of our patients, this work reinforces the need for appreciating the differential expression of deficits in subgroups of patients, which will serve to guide the appropriate selection of symptom targets for our patients. Those with cognitive deficits in the absence of amotivation may do well with strategies aimed at improving cognitive capacity and performance, while those with co-occurring amotivation may be better served by initially addressing this loss of motivation that may serve to improve their outcomes and lessen their apparent cognitive deficits.
Table 6-1. Participant Demographics and Clinical Characteristics (n=69)

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<td>Duration of illness (years)</td>
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</tr>
<tr>
<td>Antipsychotic medication class (Atypical : Typical : Both)</td>
<td>58 : 8 : 3</td>
</tr>
<tr>
<td>CPZ equivalents (mg)</td>
<td>458.2 (258.2)</td>
</tr>
<tr>
<td>Positive symptom severity (SAPS)</td>
<td>11.8 (11.8)</td>
</tr>
<tr>
<td>Negative symptom severity (SANS)</td>
<td>24.4 (17.3)</td>
</tr>
<tr>
<td>Diminished expression severity (SANS)</td>
<td>7.6 (7.0)</td>
</tr>
<tr>
<td>Amotivation severity (SANS)</td>
<td>9.5 (7.5)</td>
</tr>
<tr>
<td>Apathy severity (AES)</td>
<td>34.1 (8.0)</td>
</tr>
<tr>
<td>Intrinsic motivation (QLS)</td>
<td>3.2 (1.5)</td>
</tr>
<tr>
<td>TOMM Trial 1 score</td>
<td>45.6 (4.5)</td>
</tr>
<tr>
<td>Depression score (CDSS)</td>
<td>2.5 (3.0)</td>
</tr>
<tr>
<td>Cognition composite Z-score (BACS)</td>
<td>-1.6 (1.2)</td>
</tr>
<tr>
<td>Verbal memory Z-score</td>
<td>-1.0 (1.3)</td>
</tr>
<tr>
<td>Working memory Z-score</td>
<td>-1.3 (1.0)</td>
</tr>
<tr>
<td>Measure</td>
<td>Score</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Motor speed Z-score</td>
<td>-1.2 (1.3)</td>
</tr>
<tr>
<td>Verbal fluency Z-score</td>
<td>-0.6 (1.2)</td>
</tr>
<tr>
<td>Attention/Processing speed Z-score</td>
<td>-1.2 (1.0)</td>
</tr>
<tr>
<td>Executive function Z-score</td>
<td>-0.6 (1.2)</td>
</tr>
<tr>
<td>Extrapyramidal symptom severity (SARS)</td>
<td>0.9 (2.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CPZ – Chlorpromazine; SAPS – Scale for the Assessment of Positive Symptoms; SANS – Scale for the Assessment of Negative Symptoms; AES – Apathy Evaluation Scale; QLS – Quality of Life Scale; TOMM – Test of Memory Malingering; CDSS – Calgary Depression Scale for Schizophrenia; BACS – Brief Assessment of Cognition in Schizophrenia; SARS – Simpson Angus Rating Scale.
Table 6-2. Bivariate correlations between motivation and cognitive test performance

<table>
<thead>
<tr>
<th></th>
<th>Intrinsic Motivation (r)</th>
<th>Apathy (AES) (r)</th>
<th>Amotivation (SANS) (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BACS Composite</td>
<td>-.35**</td>
<td>-.33**</td>
<td>-.42***</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>.27*</td>
<td>ns</td>
<td>-.24*</td>
</tr>
<tr>
<td>Working Memory</td>
<td>ns</td>
<td>ns</td>
<td>-.33**</td>
</tr>
<tr>
<td>Motor Speed</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>.42***</td>
<td>-.40**</td>
<td>-.50***</td>
</tr>
<tr>
<td>Attention/Processing Speed</td>
<td>.24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ns</td>
<td>-.24&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Executive Function</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns. not significant; * p<.05; ** p<.01; *** p<.001; <sup>a</sup> p=.050; <sup>b</sup> p=.051.
Table 6-3. Bivariate correlations for effort with motivation and cognitive test performance

<table>
<thead>
<tr>
<th></th>
<th>(r)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrinsic Motivation</strong></td>
<td>.37**</td>
</tr>
<tr>
<td><strong>Apathy (AES)</strong></td>
<td>-.29*</td>
</tr>
<tr>
<td><strong>SANS Amotivation</strong></td>
<td>-.31**</td>
</tr>
<tr>
<td><strong>BACS Composite</strong></td>
<td>.39**</td>
</tr>
<tr>
<td><strong>Verbal Memory</strong></td>
<td>ns</td>
</tr>
<tr>
<td><strong>Working Memory</strong></td>
<td>.26*</td>
</tr>
<tr>
<td><strong>Motor Speed</strong></td>
<td>ns</td>
</tr>
<tr>
<td><strong>Verbal Fluency</strong></td>
<td>.41***</td>
</tr>
<tr>
<td><strong>Attention/Processing Speed</strong></td>
<td>.30*</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
<td>.34**</td>
</tr>
</tbody>
</table>

ns. not significant; * p<.05; ** p<.01; *** p<.001.
Table 6-4. Predictors of effort test performance

<table>
<thead>
<tr>
<th>Step</th>
<th>R^2 change</th>
<th>Beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Intrinsic motivation and global cognition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. BACS composite score</td>
<td>.15</td>
<td>.30</td>
<td>.014</td>
</tr>
<tr>
<td>2. Intrinsic motivation</td>
<td>.06</td>
<td>.27</td>
<td>.024</td>
</tr>
<tr>
<td><strong>B Intrinsic motivation and verbal fluency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Verbal fluency</td>
<td>.17</td>
<td>.31</td>
<td>.013</td>
</tr>
<tr>
<td>2. Intrinsic motivation</td>
<td>.05</td>
<td>.24</td>
<td>.049</td>
</tr>
<tr>
<td><strong>C Intrinsic motivation and executive function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Intrinsic motivation</td>
<td>.14</td>
<td>.31</td>
<td>.007</td>
</tr>
<tr>
<td>2. Executive function</td>
<td>.07</td>
<td>.28</td>
<td>.017</td>
</tr>
<tr>
<td><strong>D Intrinsic motivation and attention/processing speed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Intrinsic motivation</td>
<td>.14</td>
<td>.37</td>
<td>.002</td>
</tr>
<tr>
<td>2. Attention/processing speed</td>
<td>-</td>
<td>-</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns. not significant
**Table 6-5. Participant Demographic and Clinical Characteristics for NE and LE groups**

<table>
<thead>
<tr>
<th></th>
<th>NE (n=61)</th>
<th>LE (n=8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (S.D.)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>38.3 (10.2)</td>
<td>36.4 (11.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>41 : 20</td>
<td>7 : 1</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>15.3 (10.8)</td>
<td>11.8 (12.4)</td>
<td>ns</td>
</tr>
<tr>
<td>CPZ equivalents (mg)</td>
<td>445.1 (256.8)</td>
<td>558.0 (263.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Positive symptom severity (SAPS)</td>
<td>11.8 (11.6)</td>
<td>12.1 (13.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Negative symptom severity (SANS)</td>
<td>22.6 (14.9)</td>
<td>37.5 (28.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Diminished expression severity (SANS)</td>
<td>6.8 (6.2)</td>
<td>13.6 (10.0)</td>
<td>.015</td>
</tr>
<tr>
<td>Amotivation severity (SANS)</td>
<td>9.0 (6.4)</td>
<td>13.6 (13.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Apathy severity (AES)</td>
<td>33.5 (7.4)</td>
<td>38.9 (11.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Intrinsic motivation (QLS)</td>
<td>3.4 (1.4)</td>
<td>2.4 (2.0)</td>
<td>ns</td>
</tr>
<tr>
<td>TOMM Trial 1 score</td>
<td>46.9 (2.5)</td>
<td>35.6 (4.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression score (CDSS)</td>
<td>2.7 (3.1)</td>
<td>0.9 (1.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Extrapyramidal symptom severity (SARS)</td>
<td>0.9 (2.0)</td>
<td>0.9 (1.7)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Abbreviations: refer to Table 6-1; ns. not significant.
Table 6-6. Cognitive test performance profiles for NE and LE groups

<table>
<thead>
<tr>
<th></th>
<th>NE (n=61)</th>
<th>LE (n=8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
<td></td>
</tr>
<tr>
<td>Cognition composite Z-score</td>
<td>-1.5 (1.1)</td>
<td>-2.7 (1.6)</td>
<td>.014</td>
</tr>
<tr>
<td>Verbal memory Z-score</td>
<td>-1.0 (1.3)</td>
<td>-1.3 (1.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Working memory Z-score</td>
<td>-1.2 (1.0)</td>
<td>-1.7 (1.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Motor speed Z-score</td>
<td>-1.2 (1.3)</td>
<td>-1.7 (1.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Verbal fluency Z-score</td>
<td>-0.5 (1.1)</td>
<td>-1.3 (1.8)</td>
<td>(.088)</td>
</tr>
<tr>
<td>Attention/Processing speed Z-score</td>
<td>-1.1 (1.0)</td>
<td>-2.1 (0.9)</td>
<td>.012</td>
</tr>
<tr>
<td>Executive function Z-score</td>
<td>-0.4 (0.9)</td>
<td>-2.0 (1.9)</td>
<td>.001</td>
</tr>
</tbody>
</table>

ns. not significant.
Figure 6-1. Cognitive test performance profiles for Normal Effort and Low Effort groups.

Global cognition represents BACS composite Z-score, while individual cognitive domains represent standardized Z-scores for the respective cognitive tests. Significant group differences are marked (* p < .05; ** p < .01; a. p = .088).
Chapter 7

7 Discussion

7.1 Summary of Results

The results of the investigations described in the previous chapters demonstrate several key findings with regards to the determinants of community functioning in schizophrenia and the relationship between motivation and cognitive functioning seen in this illness. First, although several symptoms that comprise the psychopathology of schizophrenia exhibit significant correlations with cross-sectional functioning, when examining their concurrent contribution, the severity of motivational deficits appears to be the greatest predictor of functioning, with limited to no additional contribution from other symptoms. From both our pilot study, as well as the much larger extension of that initial work, motivational deficits accounted for a substantial proportion of the variance in cross-sectional community functioning (between 44% and 48%). Notably, this contribution remained stable across separate assessments over the course of our one-year longitudinal study. In contrast to our hypotheses and existing literature in the field, cognitive deficits did not appear to consistently offer additional predictive value towards cross-sectional functioning. Similarly, contrary to our initial hypothesis, anticipatory pleasure did not correlate with community functioning cross-sectionally. Moreover, examinations of alternative hypothetical models for the determination of cross-sectional functioning, whereby cognition or other symptoms were considered before motivational deficits, revealed that the inclusion of other symptoms did not improve our ability to predict functioning in schizophrenia, nor did they offer a significant predictive role when also considering motivational deficits in the final models.

In our investigations of the determinants of longitudinal community functioning in stable outpatients with schizophrenia over the course of one year, we also moved beyond simply
assessing individual correlations by examining the concurrent contribution of discrete symptom domains at baseline in determining longitudinal community functioning, both in terms of global functioning and within discrete functional domains. Consistent with our hypothesis, motivational deficits emerged as the most reliable determinant of longitudinal community functioning, accounting for between 43% and 58% of the variance in future community functioning. Moreover, motivational deficits emerged as the most significant predictor of discrete domains of functioning, although with differential contributions across domains. Motivational deficits contributed substantially to the prediction of longitudinal interpersonal functioning (up to 54%), and somewhat less with regards to role functioning (up to 29%) and community participation (up to 31%). In contrast to previous findings in the field, cognitive deficits did not offer any consistent additional predictive value with regards to longitudinal community functioning. Cognition only appeared to offer a relatively small contribution towards prediction of cross-sectional and longitudinal community participation. Interestingly, although not a significant determinant towards global longitudinal functioning, positive symptoms also emerged as a secondary contributor to longitudinal role functioning and community participation. Importantly, examinations of alternative hypothetical models for the determination of longitudinal functioning, with consideration of the contributions of cognition or other symptoms prior to motivational deficits, did not improve our ability to predict future community functioning in schizophrenia. Overall, our findings from these studies examining the determinants of community functioning in stable outpatients with schizophrenia suggest that the constellation of symptoms evaluated in these studies are able to account for approximately half of the variance in functioning observed in these individuals, with motivational deficits standing as the most reliable predictor. However, what remains unresolved are the factors that contribute to the remaining variance in functioning seen in schizophrenia.
Our final study investigated the relationships between motivational deficits, effort exerted during cognitive testing, and cognitive dysfunction seen in schizophrenia. We found that motivation in schizophrenia was significantly correlated with cognitive performance, with this relationship driven primarily by verbal fluency. In line with previous findings of a relationship between motivation and verbal fluency, our findings suggest that this domain of cognitive function may be particularly dependent on the individual’s level of motivation for adequate performance. Further, PVT performance (putatively indexing effort exerted during cognitive testing) was related to both motivational deficits and cognitive performance across several domains, although PVT performance appeared to be influenced by cognitive impairments seen in schizophrenia. Examining profiles of individuals exerting normal or low effort during testing revealed that differences appeared to be driven by worse cognitive performance in the low-effort group, with no differences in motivation. These findings suggest that motivation may have a differential relationship across cognitive domains, with a particular link with verbal fluency. Further, PVT scores in schizophrenia, and specifically TOMM performance in this case, appear to be influenced by cognitive impairment, raising concerns about the ability of PVTs to index effort exerted during cognitive testing in schizophrenia. Ultimately, this finding highlights the need for alternative strategies for evaluating mental effort.

7.2 Motivation in Schizophrenia – The Central Deficit

Historical descriptions of the phenomenology of schizophrenia highlighted disturbances in drive and affective expression in these patients, now subsumed under the construct of negative symptoms, and posited that these symptoms represented the hallmarks of this illness. Over the ensuing century, advances in our understanding and measurement of negative symptoms, along
with their complex interrelationships with other symptoms of schizophrenia, have led to important clarifications and reconceptualizations regarding both their phenomenology and impact on functional outcomes. The current framework for negative symptoms delineates two interrelated yet separable subdomains – diminished expression and amotivation. Symptoms of poverty of content of speech, inappropriate affect, and attentional deficits, historically considered negative symptoms, are now recognized as reflecting symptoms of disorganization seen in schizophrenia. Furthermore, clarification and deconstruction of hedonic experience in schizophrenia has suggested that anhedonia, in the strictest sense, is not a characteristic feature of schizophrenia, with current evidence pointing towards a possible anticipatory pleasure deficit, or alternatively “reduced pleasure-seeking behavior” and “beliefs of low pleasure”. Advances in affective and cognitive neuroscience have also highlighted the multifaceted nature of motivation and goal-directed behavior, with research to date in schizophrenia revealing specific deficits in reward learning, reward prediction, accurate and adaptive internal value representations, and ensuing impairments using this information to guide behavior.

The nature of the relationship between negative symptoms and other symptom domains in schizophrenia has also received considerable attention, in particular depression and cognitive dysfunction. Overall, negative symptoms have been shown to represent a separate symptom domain from depression, with any overlap between them modest and likely related to choice of rating instrument used for the assessment of depression. With regard to cognitive dysfunction, there have been important distinctions between neurocognitive and social cognitive domains, with negative symptoms existing as a related but separable symptom domain. Within negative symptoms, however, the relationship between motivation and cognitive performance has raised questions with regards to the impact of motivational deficits on cognitive impairment seen in schizophrenia. The results of our work, in conjunction with previous work in this area, serve to
highlight the complexity of the relationship between motivation and cognitive performance, whereby motivation may differentially impact cognitive domains, with some being more susceptible to the effects of amotivation. Performance validity tests, while initially believed to be insensitive to cognitive impairments and to index mental effort during testing, appear to be influenced to varying degrees by cognitive capacity in schizophrenia and beyond, suggesting that other objective strategies to index mental effort may be preferable.

In terms of functional outcomes in schizophrenia, negative symptoms figure prominently. Building on previous work in the field, the findings from our series of investigations highlight that within negative symptoms, motivational deficits appear to be the driving force that links negative symptoms to impairments in community functioning. Further, in the face of the myriad of symptoms experienced by individuals with schizophrenia, motivational deficits stand as the critical predictor of functional outcomes, both cross-sectionally and longitudinally. Other symptom domains, while important from a phenomenological perspective, appear to offer relatively smaller contributions in determining longitudinal functional outcomes in schizophrenia. Beyond our work, investigations from several groups have revealed that motivational deficits in schizophrenia, in addition to their direct relationship with functioning, also appear to play an important mediating role with regards to the relationships between neurocognition and social cognition on one hand, and functional outcomes on the other.

While negative symptoms are varied and broad in both their clinical presentation and longitudinal course, based on accumulating evidence in the field at the time, we had proposed that they could all be subsumed under the concept of avolition (i.e., amotivation) (Foussias and Remington 2010). Our current work supports this position, with motivational deficits, as the central construct, translating to impaired functional performance, a hallmark of schizophrenia’s
early stages and longer-term course. Asociality, alogia, and blunted affect represent phenotypic expressions of this pervasive motivational deficit. This hypothetical model is outlined in Figure 7-1. In the context of the broader phenomenology of schizophrenia, our work, and that of others, suggest that loss of motivation is the central deficit with regards to functional outcomes, and may also contribute to the phenotypic expression of cognitive dysfunction seen in this illness.

Figure 7-1. Schematic representation of negative symptoms with amotivation (i.e., avolition) as the central deficit.

Loss of motivation is linked to clinical presentations of negative symptoms, and translates to a functional decline observed during schizophrenia’s prodrome and over its long-term course
7.3 Subjective and Objective Assessments in Schizophrenia

Much of the work that has examined the phenomenology and outcomes of schizophrenia has relied on the use of instruments that evaluate severity of symptoms or impairment based on subjective patient reports. This goes beyond self-report measures, and includes clinician-rated instruments, which also frequently rely on individual reports upon which raters make their assessments. An additional challenge, particularly relevant for negative symptoms, is the reliance of assessments of internal experiences solely based on behavioral output (Blanchard, Kring et al. 2011; Strauss, Keller et al. 2012). This consideration applies particularly to the assessment of motivational deficits in schizophrenia through the use of either self-report or clinician-rated instruments. The SANS, for example, relies extensively on behavioral output to index motivational deficits within the avolition/apathy subscale (Andreasen 1982). In contrast, the AES, although also incorporating behavioral output into some of the scale items, includes additional items that attempt to evaluate the cognitive and emotional facets of motivation (Marin, Biedrzycki et al. 1991). These issues have also figured prominently in the reconceptualization of hedonic capacity in schizophrenia, with objective measures of in-the-moment experiences challenging long-standing notions of anhedonia as a characteristic feature in this illness (Cohen and Minor 2010; Llerena, Strauss et al. 2012). Further, this work has led to the recognition that reports of non-current feelings in the context of clinical assessments may reflect psychological and cognitive factors beyond the original intent of the assessment instrument (Horan, Kring et al. 2006; Strauss and Gold 2012). In recognition of these challenges, emerging “next-generation”
rating instruments for negative symptoms (i.e., the BNSS and the CAINS) have been designed to assess both the internal experience and behavioral outputs related to motivation, as well as consummatory and anticipatory components of hedonic experience, with the hopes of improving our understanding of these issues (Blanchard, Kring et al. 2011; Strauss, Keller et al. 2012).

There have also been several objective assessments that have been utilized in schizophrenia research that have served to address some of the issues around subjective reports. Recent evaluations of mental effort indexed through pupillary responses during cognitive task performance (Granholm, Verney et al. 2007), as well as recent strategies to index cost-effort computations (Treadway, Buckholtz et al. 2009; Gold, Strauss et al. 2013), have provided valuable insights into internal motivational states. Traditional cognitive test batteries in which objective metrics of performance are evaluated have also been frequently used, although there have emerged questions around their real-world relevance (Manchester, Priestley et al. 2004). Similarly, a performance-based functional capacity assessment methodology has been developed, in which assessments take place within the confines of a structured testing environment (Patterson, Goldman et al. 2001). However, even in the context of such structured capacity assessments, deficits observed do not always appear to translate into real-world impairments (Leifker, Patterson et al. 2011; Green, Hellemann et al. 2012). An alternative strategy that has been used effectively has been to evaluate in-the-moment experiences through the use of mobile technology, in which individuals rate their experiences in real time, thereby subverting some of the challenges with the assessment of non-current feelings (Kring and Moran 2008). Additional recent work has also explored the potential value for a video ethnography approach to evaluating neurocognitive and functional impairments in individuals with schizophrenia, with promising early findings from a very small sample (Bromley, Mikesell et al. 2012). There have also been efforts to bring the real-world environment into a structured
assessment setting, with this work hinging on the use of virtual reality technology. Such an approach has been used for comparison with standard cognitive tasks (Campbell, Zakzanis et al. 2009), to examine visuospatial navigation (Maguire, Burgess et al. 1998), driving and substance use disorders (Baumann and Sayette 2006; Calhoun and Pearlson 2012), as well as within the treatment sphere for post-traumatic stress disorder and specific phobias (reviewed in (Bohil, Alicea et al. 2011)). There has been some limited work using virtual reality for assessment and treatment in schizophrenia, with promising early findings for both cognitive deficits and motivation (Josman, Schenirderman et al. 2009; Foussias, Siddiqui et al. 2013), as well as in the realm of vocational rehabilitation (Tsang and Man 2013). Ultimately, with the concerns around subjective assessments in schizophrenia, the availability of such objective assessment strategies to evaluate important symptom domains will permit a more comprehensive, and likely more accurate, assessment of real-world deficits through which to further delineate the determinants of community functioning in schizophrenia.

7.4 The Multiple Facets of Motivation - A Path Towards Reducing Heterogeneity

Clinical assessments, akin to those used in our studies, evaluate motivation with the perspective of a unified construct. While there are some instruments that examine discrete facets of motivation such as intrinsic motivation, reward-responsiveness, and pleasure-seeking, their use within schizophrenia research has been limited and met with some inconsistent findings (Carver and White 1994; Barch, Yodkovik et al. 2008; Choi and Medalia 2010). Advances in cognitive and affective neuroscience have led to the delineation of a multifaceted framework for motivation involving four components: 1) hedonics or “liking”; 2) reward prediction and
“wanting”; 3) cost-benefit analyses and effort computation; and 4) generation and execution of a goal-directed action plan to achieve the valued outcome (reviewed in (Barch and Dowd 2010)).

As discussed earlier, much of the work in schizophrenia has focused on hedonics, reward-prediction, and the generation of goal-directed action plans, with limited work in the area of effort and cost-benefit analyses. In addition, most of this work has focused on either behavioral characterization or explorations of the neurobiological underpinnings of these discrete facets of motivation often with fMRI. However, technological barriers have limited our ability to explore the neurochemical foundations of these aspects of motivation (e.g., for D1 receptor function and its relevance to aspects of motivation).

With the multifaceted motivation framework in mind, our findings linking motivational deficits to both cognitive and functional impairments in schizophrenia suggest further delineation of the behavioral and neurobiological foundations of motivational deficits in this illness is essential as we strive to develop novel therapeutic strategies for the treatment of this illness. Through this approach, incorporating existing and novel objective strategies to assess discrete components within the multifaceted motivation framework may enable the identification of more homogeneous subgroups of individuals with schizophrenia with deficits in a specific facet of motivation, and provide insights into therapeutic brain targets for these deficits. Moreover, this may provide a means of parsing out the differential effects of motivation on cognitive performance, and enable the distinction of those individuals whose cognitive dysfunction may be a result of motivational deficits from those with bona fide cognitive deficits. Ultimately, this may lead to more effective and personalized therapeutic strategies with which to address the specific deficits individuals experience, and serve to improve outcomes for those with schizophrenia.
7.5 Limitations

As with all scientific endeavours, there are certain limitations with the approaches and findings from the investigations described in the preceding chapters that should be considered. First, with regards to our evaluations of the determinants of community functioning, we did not include a measure of social cognition in our longitudinal investigation. Given recent findings for the important role for social cognition in predicting functional outcomes in schizophrenia (Schmidt, Mueller et al. 2011), we would expect this to be an additional important predictor of community functioning. However, based on recent structural equation modeling results showing that social cognition influences functional outcomes in schizophrenia along a single pathway through motivational deficits as the final step (Green, Hellemann et al. 2012), it is likely that the addition of a measure of social cognition to our study would potentially have improved the amount of variance in community functioning that was explained, without necessarily reducing the overall impact of motivational deficits.

Further, we did not include a measure of defeatist performance beliefs, which has emerged as an important psychological factor linked to motivational deficits and negative symptoms more broadly in schizophrenia (Rector, Beck et al. 2005; Grant and Beck 2009). However, a recent examination of real-world functioning in schizophrenia revealed that while defeatist beliefs appeared to be an important contributor to negative symptoms, it was ultimately negative symptom severity that mediated the relationship between defeatist beliefs and community functioning (Horan, Rassovsky et al. 2010). In light of this, the inclusion of defeatist beliefs in the present study, while improving our understanding of the contributors of motivational deficits
in schizophrenia, would not be expected to substantially alter the predictive value of motivational deficits with regards to longitudinal community functioning.

From a psychometric perspective, as discussed above, the use of clinical measures that rely on behavioral proxies to evaluate the internal experience of motivation may confound evaluations of the relationship between motivation and functioning. We used three strategies to mitigate against this: 1) due to direct overlap in items with our clinical measure of amotivation, we removed the Intrapsychic Foundations subscale of the QLS from our determinations of functional status; 2) in the final two studies of longitudinal functioning we used the AES, rather than the SANS, as our preferred measure of amotivation, due to its inclusion of items that attempt to also evaluate the loss of motivation within cognitive and emotional spheres; and 3) we evaluated all our analyses for evidence of multicollinearity, which we did not find, suggesting that our findings were not a result of two instruments essentially measuring the same construct.

There have also been concerns around the use of the QLS as a measure of community functioning, particularly as it was originally developed as a measure of the deficit syndrome (Heinrichs, Hanlon et al. 1984). Beyond its frequent selection as a measure of functional outcome in psychopharmacology trials, including two recent large antipsychotic effectiveness trials in schizophrenia, however, the QLS has also been subjected to rigorous review within the context of an expert consensus panel on clinical measures of real-world functioning in schizophrenia (Leifker, Patterson et al. 2011). Through this examination of available clinical instruments, the QLS emerged as the highest rated comprehensive measure of real-world outcomes, with notable findings in support of its psychometric properties and sensitivity to change (Leifker, Patterson et al. 2011). Moreover, the functioning subscales of the QLS, consisting of interpersonal functioning, role function, and community participation, have also
been found to form discrete factors in line with the conceptual model of this scale (Heinrichs, Hanlon et al. 1984), and exhibit good to excellent test-retest reliability, internal consistency, and convergent validity (Lehman, Postrado et al. 1993; Simon-Abbadi, Guelfi et al. 1999; Cramer, Rosenheck et al. 2000; Kaneda, Imakura et al. 2002).

These studies examining community functioning were conducted in stable outpatients with schizophrenia or schizoaffective disorder. As expected in such a population, and in the absence of any specific intervention in our studies, there was no statistically significant change in severity of motivational deficits or overall functioning over the duration of follow-up. This limits our ability to determine if change in motivational deficits was related to change in community functioning over time, and precludes conclusions around a causal relationship. Other studies that have examined negative symptoms more broadly in the context of treatment trials, however, have identified a significant relationship between a reduction in negative symptom severity and improvement in functioning in schizophrenia (Velligan, Alphs et al. 2009; Rabinowitz, Levine et al. 2012), offering support for a causal model whereby negative symptoms in schizophrenia lead to functional impairment.

A further limitation to the present studies was that all individuals in the current sample were being treated with antipsychotic medication, which has the potential to cause or worsen some of the motivational and cognitive deficits seen in schizophrenia. In order to control for this, we conducted secondary analyses with the inclusion of extrapyramidal side effect severity as an index of the potential cognitive and motivational adverse effects of dopamine antagonism, with no change in predictors for any of our analyses or the strength of their contributions. Importantly, given that dopamine antagonists represent the cornerstone of treatment for psychotic symptoms in schizophrenia, the inclusion of individuals who are being treated with
antipsychotic medications represents a clinical reality and bolsters the generalizability of our findings. It is recognized, however, that extrapyramidal symptoms are a crude measure for the potential cognitive and motivational adverse effects of dopamine antagonism, but represent the only available approach at present. Beyond antipsychotic medication effects, other important factors that may contribute to functional impairment in schizophrenia, including environmental deprivation, personality features, self-esteem, family socioeconomic status, and education were not included in these studies.

With regards to our investigation into the relationships between motivation, effort, and cognition, we did not include a healthy or non-psychotic psychiatric comparison population, which limits our ability to draw conclusions beyond schizophrenia, and does not address the potential impact of a chronic psychiatric illness on the willingness to exert effort during cognitive testing. However, previously published worked using the TOMM suggests that those individuals in our study exhibiting normal effort had equivalent mean scores to healthy controls, traumatic brain injury subjects, and depressed subjects in other studies, while those exhibiting low effort had substantially reduced mean scores, although with no subjects in the “chance” range (i.e., approximately 50% correct) (Tombaugh 1996; Rees, Tombaugh et al. 2001). An additional limitation relates to the use of BACS subtests as measures of domains of cognition, with the limited number of tests for each domain being below the recommended number for adequately evaluating discrete constructs (Kenny, Kashy et al. 1988).

There have also been concerns with the use of cut-off scores for categorizing individuals as exhibiting low effort, as well as concerns around false positives and negatives with PVT use. Recognizing the concerns around the use of cut-off scores for dichotomizing participants into normal and low-effort groups and the potential for inappropriate classifications, we opted to
utilize both categorical and continuous analytic strategies when examining the relationships between effort and cognitive performance. We believe this offers a more balanced and conservative approach to examining these relationships. In our categorical analyses, we acknowledge that the small sample size for the low-effort group (n=8) represents a limitation. This was included, however, as this type of categorical analysis is the standard practice within PVT research, and thus enables comparison between our findings and the existing literature. Importantly, poor performance on the TOMM in our sample was not viewed as suggestive of feigned cognitive impairment by those participants, as is the case in forensic samples, as there were no advantages for performing poorly. In addition, although PVTs, including the TOMM, have frequently been used for the examination of effort during cognitive testing, the establishment of the construct validity of these instruments has been limited by the absence of a gold standard. This limitation is addressed in part in our examination of the relationship between TOMM performance and clinical measures of motivation, although a specific measure of mental effort was not included in our study. Further, the use of only trial 1 of the TOMM, although having been found to exhibit good sensitivity and specificity in relation to performance on trial 2 and the retention trial of the TOMM, represents an abbreviated form of this PVT. In addition, the use of multiple PVTs, rather than a single PVT, within the context of a neuropsychological examination would incrementally add validity to any conclusions regarding effort per se.

The sample sizes in some of our studies, particularly study one and two, are notably small, and raise the possibility that they were not adequately powered to detect significant relationships between variables. Post-hoc power analyses reveal that in study one and two, we were able to detect significant predictors in our multiple regression analyses with an $R^2 > .30$ and .33, respectively, with 80% power at an alpha = .05. These suggest that the first two studies were adequately powered to detect significant predictors that accounted for at least one-third of the
variance in functioning, although not sufficiently powered to detect less influential predictors. In study three, post-hoc power analyses reveal that the study was adequately powered (i.e., 80% power, alpha = .05) to detect significant predictors in the multiple regression analyses with: 1) an \( R^2 > .11 \) at baseline; 2) an \( R^2 > .12 \) at 6-month follow-up; and 3) an \( R^2 > .14 \) at 12-month follow-up. These results suggest that this larger study was adequately powered to identify significant predictors that would explain at least 11% of the variance in functioning in schizophrenia, and thus would stand to be clinically meaningful. In study four, post-hoc power analysis reveals that the study was adequately powered (i.e., 80% power, alpha = .05) to detect statistically significant bivariate relationships with \( r > .33 \), again consistent with detecting significant relationships that would be clinically meaningful. Additionally, despite differences in sample sizes across the three studies examining the predictors of community functioning in schizophrenia, the findings across these studies are notably similar. While there are numerical differences in the bivariate correlations between motivational deficits and functioning across studies, comparison of correlations through Fisher’s r-to-z transformation reveals that these correlations are not significantly different. Similarly, across the three assessment time points in study three, comparison of correlations between motivational deficits and functioning by way of Fisher’s r-to-z transformation reveals non-significant differences in these correlations.

Finally, we acknowledge that correlational analyses do not provide information regarding causality, but rather permit the examination of relationships between symptoms, and with functioning, in the context of hypothesized models within which these relationships are interpreted. Based on the extant literature, the prevailing model considers symptoms of schizophrenia as contributing to the ensuing functional impairment seen in the illness. There are, however, additional possibilities including: 1) functional impairment itself contributing to worsening negative symptoms, and in particular amotivation, potentially through the
reinforcement of defeatist beliefs; and 2) an as yet unidentified third factor causing motivational
deficits and functional impairment in schizophrenia. Further, in our investigation of the
relationship between motivation, effort, and cognitive test performance, the results are
interpreted in the context of a potential causal pathway whereby change in motivation leads to
change in cognitive performance, in line with previous findings of monetary incentives leading
to improved cognitive performance. It is acknowledged, however, that cognitive impairment,
and in particular memory, attention, processing speed, and executive function deficits, may lead
to a loss of motivation.

7.6 Future Directions

The results of the investigations presented here, along with other recent developments in the
field, have led to the conceptualization, and in some cases the initial stages, of future directions
of study, with a particular focus on motivational deficits and improving functional outcomes in
schizophrenia. These are explored below.

7.6.1 Development of a Novel Objective Measure of Motivation in
Schizophrenia

In light of the issues and challenges present with the use of subjective and non-current
assessments of internal experiences, coupled with technological advances, we have undertaken
the development and early behavioral testing of a novel strategy for objectively evaluating a
discrete aspect of motivation in schizophrenia. The use of objective measures of the experience
of pleasure has served to enhance our understanding of hedonic capacity in schizophrenia.
However, there is a dearth of similar methods for the measurement of motivation. Strategies to
date have involved the use of abstract representations of goals and reward, including the Cued Reinforcement Reaction Time Task (Murray, Clark et al. 2008), the Monetary Incentive Delay task (Knutson, Westdorp et al. 2000), and an evoked and representational responding task (Heerey and Gold 2007). While providing valuable insights into the neurobiology of motivation, these methods lack ecological validity i.e., they do not approximate real life situations where motivational deficits would have functional consequences for individuals with schizophrenia.

In an effort to bring ecological validity to the evaluation of motivation, we are using virtual reality technology to create a virtual environment within which to evaluate effort, i.e., the willingness to work towards a goal, in schizophrenia. Such techniques have been used previously to investigate cognitive functioning in healthy individuals and those with mild cognitive impairment (Maguire, Burgess et al. 1998; Mraz, Hong et al. 2003; Tippett, Lee et al. 2009; Tippett, Lee et al. 2009; Zakzanis, Quintin et al. 2009), and positive symptoms in schizophrenia (Freeman 2008). Our approach represents a translation of a long-standing paradigm in animal research that utilizes a progressively increasing work-to-reward ratio to evaluate motivation (Arnold and Roberts 1997). Within a virtual environment consisting of a generic city street with stores on either side, participants navigate and complete a series of common everyday tasks using a joystick, with a first-person viewpoint displayed on a large widescreen display. The objective is for individuals to obtain points by completing tasks in the virtual city, which in the context of the research study they are instructed is related to monetary compensation they will receive. However, after successfully obtaining points for task completion, the required number of tasks that must be completed to obtain the next unit of reward (e.g., 100 points) increases in a manner directly analogous to the animal progressive ratio paradigm. Objective metrics of willingness to work including the total points earned by
individuals, the number of tasks they complete, as well as the rate at which they proceed to complete tasks.

The first stage of this work consists of behavioral validation and characterization of performance in schizophrenia and matched healthy control participants. Subsequently, in order to evaluate the neurobiological substrates that support this willingness to work for reward, we will carry out functional and structural brain imaging while subjects perform this virtual reality task. The results of this work are expected to reveal the network of brain regions that serve to support such effortful work within the context of a virtual world, and guide future explorations of therapeutic interventions including brain stimulation and pharmacologic strategies that may serve to ameliorate deficits in the effortful pursuit of goals that are emerging as a feature of schizophrenia (Foussias, Siddiqui et al. 2013).

7.6.2 Behavioural and Neurobiological Characterization of the Multiple Facets of Motivation in Health and Illness

The presence and importance of motivational deficits across numerous neuropsychiatric illnesses, as described above, suggests that investigations across illness populations may offer valuable insights into the underlying neurobiological pathways that lead to motivational deficits, and provide avenues for therapeutic interventions across illnesses. To date, however, neurobiological investigations of motivational deficits have focused primarily on single facets of motivation and in single illness populations compared to healthy adults. From these, reward valuation has been linked with amygdala, ventral striatum, midbrain, ventromedial prefrontal cortex, orbitofrontal cortex, and lateral prefrontal cortex function (McClure, Laibson et al. 2004; Barch and Dowd 2010; Lawrence, Goerendt et al. 2011). Effort valuation, on the other hand, has
been linked with nucleus accumbens, amygdala, and anterior cingulate cortex functioning (Salamone, Correa et al. 2009; Barch and Dowd 2010). Across several studies, reward expectancy and prediction error has been linked to dorsal and ventral striatum, limbic system, medial and lateral PFC, and OFC activity (Juckel, Schlagenhauf et al. 2006; Pessiglione, Seymour et al. 2006; Murray, Corlett et al. 2008; Pizzagalli, Holmes et al. 2009; van Eimeren, Ballanger et al. 2009; Schonberg, O'Doherty et al. 2010; Waltz, Schweitzer et al. 2010). Further, responsiveness to reward attainment has been linked to ventral striatum, medial prefrontal cortex, dorsolateral prefrontal cortex, and orbitofrontal cortex function (Crespo-Facorro, Paradiso et al. 2001; Paradiso, Andreasen et al. 2003; McCabe, Cowen et al. 2009; Pizzagalli, Holmes et al. 2009; Dowd and Barch 2010). Additionally, investigations of reward learning have implicated basal ganglia – orbitofrontal cortex interconnections and the amygdala in this facet of motivation (Frank, Seeberger et al. 2004; Frank and Claus 2006; Talmi, Seymour et al. 2008). While highly informative, these findings underscore the complexity of the human motivational system, and the apparent overlap in brain regions associated with multiple aspects of motivation. However, as these studies each investigated only a single motivation construct, the findings may represent a combination of specific brain regions for a particular motivation construct, as well as accessory areas in related motivational constructs that were concurrently recruited in these isolated tasks. The potential lack of specificity from this approach makes conclusions around the role of a particular brain region within the larger framework of the motivational system difficult.

In an effort to systematically evaluate the multiple facets of motivation and deficits therein in neuropsychiatric illnesses, we will undertake a comprehensive behavioural and neurobiological investigation of the human motivational system. The initial goals of this work will be to: 1) evaluate through objective paradigms the performance of healthy adults, individuals with
schizophrenia, and those with major depressive disorder, across several facets of motivation, and their relationships with behavioral, clinical, and self-report measures; and 2) evaluate the neurobiological correlates of specific motivation constructs through a multimodal imaging approach consisting of functional and structural brain imaging. Following this initial phase, the feasibility of additional participant groups in which motivational deficits figure prominently, including individuals with Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease, will be evaluated.

To our knowledge, there has not been a comprehensive evaluation of the multiple facets of motivation concurrently in any clinical population, let alone across multiple neuropsychiatric illnesses and in healthy adults. Given the complexity of the motivational circuitry and the functional consequences associated with motivational deficits across neuropsychiatric illnesses, there is a need for a clear delineation of normal human motivational circuitry and its perturbations in illness. We anticipate this approach will provide a more precise understanding of the neurobiology of discrete components of motivation, and further, provide valuable biological targets for therapeutic interventions.

7.6.3 Novel Treatment Strategies for Motivational Deficits in Schizophrenia

The negative symptoms, and in particular the motivational deficits that are central to their functional consequences, represent an area of unmet therapeutic need in schizophrenia. As reviewed earlier, pharmacologic agents have offered minimal and inconsistent benefit for these deficits. There has been, however, some accumulating evidence over several decades for the potential benefit of dopamine agonists for the treatment of negative symptoms in schizophrenia.
(Jaskiw and Popli 2004). These findings are in keeping with historical and contemporary notions that schizophrenia may fundamentally represent a hypodopaminergic disorder (Remington, Agid et al. 2011). In light of this, a pilot study evaluating the safety and efficacy of dopamine agonist augmentation of antipsychotic treatment in schizophrenia is currently being undertaken. In conjunction with this, evaluations of individuals’ performance on our virtual reality effort task (described above) pre- and post-treatment will provide valuable information with regards to the sensitivity of this novel objective task to change in symptom severity over the course of treatment.

However, it remains unclear whether pharmacologic agents alone are sufficient to effect an improvement in the motivational deficits in schizophrenia, or whether this will translate into real-world functional gains for these individuals. Treatment guidelines from other psychiatric illnesses, including depression and attention deficit disorder, suggest that combined pharmacologic and psychosocial/psychotherapeutic interventions show some evidence of improved efficacy compared to either treatment alone (Segal, Kennedy et al. 2001; Nutt, Fone et al. 2007). In addition, there has been accumulating evidence suggesting that virtual reality therapy exhibits efficacy for the treatment of psychiatric disorders including post-traumatic stress disorder, specific phobias, and some early benefit for vocational rehabilitation in schizophrenia (Bohil, Alicea et al. 2011; Tsang and Man 2013). These findings raise the possibility that our virtual reality task, in addition to evaluating willingness to work towards a goal, if administered as a structured training environment with increasing effort demands across treatment sessions may offer therapeutic benefit for the treatment of motivational deficits in schizophrenia. What will need to be determined following our pilot study with dopamine agonist augmentation in schizophrenia is the potential for combining this pharmacologic strategy with such a virtual
reality therapeutic intervention, and the systematic evaluation of this approach in the context of a clinical trial.
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